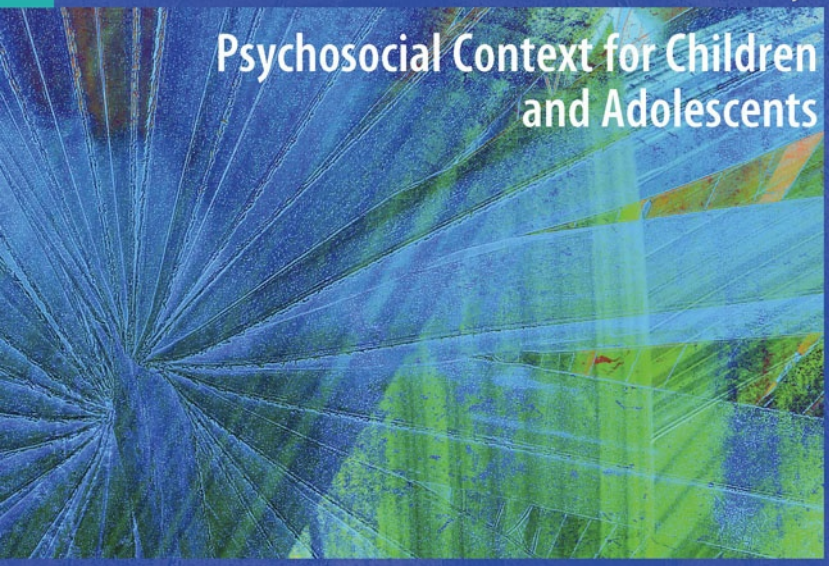
ISSUES IN CLINICAL CHILD PSYCHOLOGY

Kenneth P. Tercyak
Editor

Handbook of Genomics and the Family

Psychosocial Context for Children and Adolescents



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Handbook of Genomics and the Family

Psychosocial Context for Children and Adolescents

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To my wife, Randi, and our children, Sam, Anna, and Ryan, for their support and good humor always.

Preface

Today, individuals have greater access to information about their health than ever before (Randeree, 2009; Eysenbach, 2008). Much of this change is due, in large part, to advances in biotechnology and the sequencing of the human genome (Manolio & Collins, 2009). It is now possible, for example, for individuals to log onto the Internet and, for a fee of several hundred dollars, order an at-home DNA collection kit and have the results of a myriad of genetic tests delivered directly to their e-mail inbox (Gurwitz & Bregman-Eschet, 2009). In some cases, these test results may indicate personal risk for common chronic diseases, such as certain forms of cancer, diabetes, cardiovascular disease, and several others. Companies marketing these test kits often claim that promoting greater access to and awareness of the association between genes and health, and one's genetic susceptibilities to disease, leads to more proactive and insightful methods of individual health management (Hogarth, Javitt, & Melzer, 2008). Moreover, it is consistent with an emerging trend in medicine – that of consumer-oriented medicine – which places health information tools directly in the hands of patients under the premise of fostering better patient–provider collaboration (Silvestre, Sue, & Allen, 2009).

Though the principles behind this direct-to-consumer approach to genetics seem laudable and perhaps even exciting, there is considerable controversy as to what, if any, utility the information actually holds (Geransar & Einsiedel, 2008; Wasson, Cook, & Helzlsouer, 2006). Unlike genetic tests that are diagnostic (e.g., chromosome analysis for Down syndrome) or highly predictive (e.g., *BRCA1* and *BRCA2* testing for hereditary breast–ovarian cancer risk), this new wave of presymptomatic predictive genetic tests for common disease yields results that are much more uncertain because the statistical models on which they are presently based are imperfect and with limited data (Ng, Murray, Levy, & Venter, 2009).

The above scenario raises many questions for today's health-care consumers. For example, for whom is this information applicable, and for what populations or subpopulations is it not? Under what circumstances might this information be useful, and when should it be disregarded as irrelevant? And perhaps most importantly, what, if anything, can be done in light of information about personal genetic risk to effectively lower the odds of becoming sick and raise the odds of staying healthy?

Because the prevalence of most diseases varies as a function of age, gender, race/ethnicity, and other personal characteristics, answers to these questions are complex and many are just beginning to be understood (Khoury et al., 2009). Some experts have concluded that the answers to such questions remain out of reach at the present time and may continue to be elusive for another 5–10 years (Frazer, Murray, Schork, & Topol, 2009). Yet, twenty-first century health-care consumers, providers, and policy makers face these choices now about incorporating personal genetic information into health management and often do so without a complete and accurate understanding of the potential impact of their decisions on multiple levels (Carlson, 2009).

As a society, we are just beginning to come to terms with how information from the revolution in genetics affects the health and well-being of the population (Ozdemir et al., 2009; Kunstmann & Epplen, 2006) and that of its most valuable resource – our children (Duncan, Savulescu, Gillam, Williamson, & Delatycki, 2005). In many respects, the above scenario captures an ongoing tension in genetics at present – one resting at the nexus of biotechnology, human genome science, and our ability to safely and effectively deploy and translate the results of genetic tests for individuals in full scope of their meaning to human health (Editorial, 2008; Kaiser, 2007). Traditionally, this latter role was performed through the health-care system by professionals trained and board-certified in medical genetics or genetic counseling. As genetic testing proliferates both within and outside of the health-care environment, it challenges traditional models of genetic health-care delivery and calls for a means to respond to this reality (Deverka, Doksum, & Carlson, 2007; Woodcock, 2007).

Though we do not yet know how rapidly this change will take place, or what form it may eventually assume, it is reasonable to anticipate that change is coming. Genetic testing is no longer confined, for example, to the realm of obstetrics and the choices that pregnant couples face when learning about the well-being of their unborn child. Likewise, it is no longer confined to pediatrics, the diagnosis and care of children with very rare diseases, and the coping experiences of parents who may have passed on disease-conferring risks to offspring. Today, genetics is part of virtually all medical specialties, particularly those involved in delivering primary care services to patients (Baird et al., 2009).

This emerging paradigm shift in the way that individuals may access genetic information (e.g., in clinical settings or online), and choose to interact with it (e.g., with or without the guidance of a qualified health-care professional), serves as an important referent point for this volume. Simultaneously, this is a landmark era of opportunity for social and behavioral scientists to help translate basic science discoveries from the genetics lab into better patient care and improved health outcomes for all (Patenaude, Guttmacher, & Collins, 2002), including young people (Tercyak, 2009; McBride & Guttmacher, 2009). It is also a time to examine robust and interrelated sets of questions surrounding which individuals might be interested in learning information about their personal genetic risk for disease, how individuals process and understand genetic risk

information, and (most importantly) how they may change their health behaviors in response to such news (McBride et al., 2008).

Health psychology, or psychology's contribution to the interdisciplinary fields of behavioral and preventive medicine, is often aligned with the activities of primary care (Kessler, 2009). At its core, health psychology advances knowledge and understanding about the relationship between behavior and health, health promotion, and disease prevention (Sallis, Owen, & Fotheringham, 2000). As a discipline, health psychology has been translating the genetic aspects of behavior–disease relationships to health for more than a decade (Plomin, 1998; Lerman, Croyle, Tercyak, & Hamann, 2002). Health psychology often works alongside other medical and public health specialties to further the pursuit of knowledge in this area, most notably with those working in the domains of gene–behavior relationships and gene–health relationships. Together, these and other disciplines have helped to solidify and redefine a biopsychosocial model of medicine by integrating the social, psychological, and behavioral dimensions of health and health care (Engel, 1977; McClearn, 2004) with a new and emerging emphasis on genetics and personalized medicine (see Figure 1).

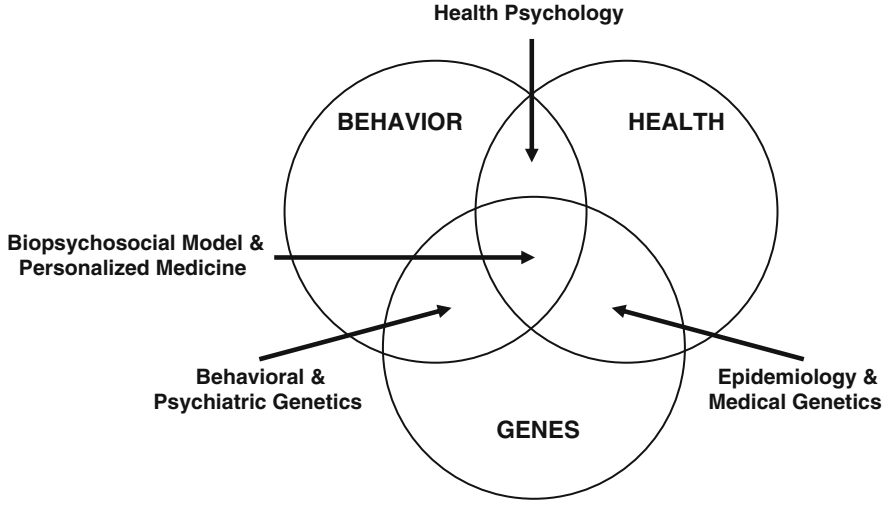

Figure 1. Interrelationships among the study of genes, behavior, and health.

Personalized medicine (also called systems medicine) has been defined as the application of molecular genetic information to health-care, with the goal of tailoring medicine to better meet the needs of given individuals (Janssens & van Duijn, 2008). Endeavors subsumed under the rubric of personalized medicine are numerous and include predictive genetic tests to identify persons at risk of developing certain health conditions, preventive therapies that are specific to this risk profile to help reduce it, and evidence-based approaches that are most likely to be successful in treating disease states that are based on risk analyses (Janssens & van Duijn, 2008).

One of the greatest and most anticipated potentials for personalized medicine is its impact on the prevention of disease states, especially when carried out among unaffected, healthy individuals (Kawamoto, Lobach, Willard, & Ginsburg, 2009). If one follows a personalized medicine approach incorporating predictive genetic testing to its logical conclusion, then primary prevention of disease before any signs of that disease may emerge is a highly laudable goal. Though there has been progress toward reaching this outcome, significant hurdles in medical education and health-care policy remain (Federoff & Gostin, 2009). Few health-care providers are well trained, for example, in behaviorally based approaches to disease prevention, and there is often too little time and incentive for providers to make prevention more of a priority (Pollak et al., 2008). There is currently thin evidence that incorporating the results of genetic tests and other biomarkers of potential harms to health into prevention-based health-care messages motivates or produces stronger or longer lasting behavior change (McClure, 2001). In light of this, some have questioned the wisdom of this approach over more traditional and effective forms of risk assessment (e.g., taking a detailed family health history) and noted the value of more integrated perspectives within primary care (Gartner, Barendregt, & Hall, 2009; Rich et al., 2004).

A majority of the work in personalizing medicine takes place with a focus on adults. For example, there has been a proliferation of genetic tests that may be used in the identification of adult cancer risks (e.g., *BRCA1* and *BRCA2* mutations) (Willey & Cocilovo, 2007; Arsanious, Bjarnason, & Yousef, 2009) and likely response to chemotherapy and other treatment regimens (e.g., genetic tumor profiling) (Slodkowska & Ross, 2009). Yet, we are reminded that much of the history of genetics in medicine is focused on the health and well-being of children, adolescents, and their families (Rimoin & Hirschhorn, 2004). We are also reminded of the special considerations that must take place anytime that children and adolescents are involved in therapeutic and nontherapeutic clinical trials, and that this can impact the pace of discovery in pediatrics (Wendler & Forster, 2004). Within the context of personalized medicine approaches to health and health-care, and its focus on primary prevention, far more work is needed to help translate these results to children. Though there are some promising steps forward in childhood cancer (Rabin, Man, & Lau, 2008), asthma (Koster et al., 2009), epilepsy (Glauser, 2002), and psychiatry (Stein & McGough, 2008), more are needed (Leeder, 2003). The disparities in personalized medicine research taking place with and for adults relative to similar work taking place with and for children and adolescents are striking.

Perhaps one way to help advance this conversation might be to adopt more of a lifespan perspective on health (commonly used in the field of developmental psychology) to facilitate our understanding of variations and nuances in the timing and onset of disease processes (Eaton, 2002; Tercyak, 2008): the National Children's Study is but one example of this perspective (Branum et al., 2003). Though such works take many years to accomplish, the potential benefits to society that result from exploration of chains of biological and environmental processes (e.g., epigenetic

processes), and the importance of early-life experiences in the programming of adult health, are substantial (Solomons, 2009; Wadhwa, Buss, Entringer, & Swanson, 2009). These experiences include the family environment in which children are raised, the quality of the health-care received pre- and post-natally, the diet, the physical activity, and other lifestyle behaviors established early on that may track into adulthood, and the decisions and actions that children, adolescents, and their families take that promote or compromise both short- and long-term health outcomes (Shonkoff, Boyce, & McEwen, 2009). When considered in conjunction with genetics and the results of genetic tests, these factors may someday bring us a step closer to realizing the potential of personalized medicine for young people (Arnold & Jones, 2009; Balistreri & Helton, 2009). The results of large-scale gene sequencing efforts answering fundamental questions about the heritability of common disease will further drive this discovery process (Maher, 2008).

Thus, it is timely to reflect on the state of the science in health psychology and related disciplines that are concerned with translations and linkages among genes, behavior, and health and, specifically, the impact of the rapid emergence of such data for children, adolescents, and their families. In doing so, it is important to keep in mind continuity and discontinuity in the use of the terms "genetic" and "genomic" as typically encountered in the literature. Defined, genetics usually refers to the study of single genes and their impact on health. Genomics, by contrast, refers to the study of all genes and the interactions of genes with other genes and the environment to impact health. Both genetics and genomics are important to the discourse on this topic, as single genes, multiple genes, and their interaction with the environment hold meaning for healthy development among families.

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Contents

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Part IV Emerging Issues

Introduction

This handbook is divided into four major parts, each containing original chapters authored by leading scientists and practitioners in their fields of study. The topics of these chapters were carefully selected. All seek to provide the reader with a comprehensive understanding of how the health and quality of life of children, adolescents, and their families may influence and be influenced by rapid developments transpiring in medical genetics and genomics.

The book begins with an introduction to genome health science. These chapters seek to educate the reader about foundational issues in human genetics and genomics, including how understanding the pattern and prevalence of diseases in childhood is enriched by knowledge of genetic and genomic substrates. Importantly, these chapters lay the foundation for recognizing and interpreting the manner in which modifiable factors, such as environment and behavior, interact with genes to affect child and adolescent health.

The book's next part seeks to address broad, cross-cutting issues that surround advanced knowledge of genetics and genomics with attention to the provision of services that can help meet the needs of families. The questions taken up in this part necessarily reflect family-centered perspectives, as families are often the cornerstones of clinical genetics. These chapters explore details of how one can, for example, conceptualize families as interconnected sets of individuals interacting with genetic information on varying levels and at varying points throughout the family life cycle. By promoting the reader's understanding of competing forces acting on families' behaviors and the role of family behavior on genetic information-seeking, the chapters shape key processes in education and counseling about genes and health. It is necessary to recognize that service provision in genetics and genomics includes, but is not limited to, traditional clinical encounters. The chapter authors acknowledge some community-based perspectives as well, recognizing recent paradigm shifts toward incorporating genetics and genomics into public health. Over time, the context in which children, adolescents, and their families will interact with genetic health information is expected to grow. Preparing the next generation of social and behavioral scientists and heath-care clinicians to operate more effectively within these contexts is essential.

A significant portion of this book covers contemporary issues related to what is known about the role of genetics and genomics in health and disease. The third part of the book adopts a primarily disease-focused orientation toward that discussion, covering some of the leading health conditions affecting young people. This includes genetic diseases and genetic disease risks that may be present at the earliest stages of life, as well as those that emerge throughout childhood and beyond. Given the widespread prevalence of many of these diseases in our society (e.g., diabetes, obesity, and cardiovascular disease) and the important role that lifestyle behaviors play in prevention, an understanding of the interplay between genetic risk and environmental factors mediating that risk is essential to positive outcomes. Among the outcomes that these chapters consider are family members' social and behavioral responses to knowledge about the genetic origins of health and disease and potential consequences (both positive and negative) that can be associated with that understanding. In many cases, the full implications of such knowledge for children and families have yet to be well-documented. Nevertheless, these chapters serve as reminders of how vital it is to continue to generate new insights to close that gap through social and behavioral investigation, laying the groundwork for improved translation into pediatric medicine.

And finally, this book addresses frontier-like issues surfacing in the wake of the genetics and genomics revolution in health. This is a diverse range of topics, including attention to how the discovery of molecular markers of disease risk and disease progression can inform both the prevention and the treatment of childhood health conditions. Doing so necessarily requires a thorough understanding of ethical, legal, social, and policy frameworks and implications of any such progress. Their meaning to children, adolescents, and families warrants special consideration, including considering issues such as cognitive capacity to participate in research and clinical endeavors involving genetic and genomic testing, decisional capacity and the legal standing of minors and their parents as legal representatives and caretakers, and the adequacy of protections and safeguards against numerous forms of harm. Like most complex issues, input from stakeholders with diverse backgrounds and perspectives could lead to more well-informed solutions. The enactment of these solutions will require a cadre of highly versatile practitioners operating across traditional professional boundaries. Toward that end, the book closes with a discussion of training and collaboration in the field of psychology and the role of the social and behavioral sciences more generally in the use of genetic and genomic information to benefit pediatric medicine and public health.

About The Editor

Kenneth P. Tercyak is an associate professor in the Division of Health Outcomes and Health Behaviors of the Department of Oncology and in Pediatrics at the Georgetown University Medical Center in Washington, DC. Dr. Tercyak received his bachelor of arts degree (1992) in psychology with distinction and a minor in American civilizations from the University of Pennsylvania. He trained as a pre-doctoral research fellow at the Yale Child Study Center before going on to earn his doctor of philosophy (1998) in clinical psychology from the University of Florida's College of Public Health and Health Professions with specialization in clinical child, pediatric, and family psychology. Dr. Tercyak completed additional clinical training at the Mailman Center for Child Development at the University of Miami School of Medicine (1997–1998) and postdoctoral research training in cancer prevention and control at the Lombardi Comprehensive Cancer Center (1998–2000).

Dr. Tercyak's research has focused on several areas of cancer prevention and control among children, adolescents, and families. This includes a program of research on the social and behavioral aspects of genetic testing for hereditary cancer syndromes among parents, developing and testing strategies for informed decision making and communication support in cancer genetics, and evaluating long-term outcomes among children growing-up in environments affected by familial cancer. Dr. Tercyak's other investigations have included a focus on biopsychosocial influences on youth smoking adoption, pediatric cancer survivorship, adolescent health promotion, and genetic testing for common diseases of childhood. He has received continuous funding by the National Institutes of Health since 1998, including a National Research Service Award and Research Career Development Award from the National Cancer Institute, and funding from the National Human Genome Research Institute's Ethical, Legal, and Social Implications research program and the Division of Cancer Control and Population Sciences at the National Cancer Institute.

Dr. Tercyak's scholarly contributions consist of more than 75 journal articles and book chapters. He has delivered invited presentations at a number of scientific organizations, including the American Society of Human Genetics, American Society of Preventive Oncology, Cincinnati Children's Hospital Medical Center, Dana-Farber Cancer

Institute, Memorial-Sloan Kettering Cancer Center, National Human Genome Research Institute, Seattle Children's Hospital, Society for Adolescent Medicine, Society of Behavioral Medicine, and St. Jude Children's Research Hospital.

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Part I

Introduction to Genomics

1

Key Concepts in Human Genomics and Epidemiology

OFFIE P. SOLDIN and CHRISTOPHER A. LOFFREDO

INTRODUCTION

Every expectant parent hopes for a healthy newborn infant and wants their baby to grow up healthy and happy. When serious child health problems become apparent, it is natural to ask why: What could have happened? Could this have been prevented? What caused this? Depending on the nature of the problem, suspicion may come to rest initially on prenatal exposures and environmental factors, and indeed for centuries this was the only available avenue of inquiry. It has been well known, for example, that heavy alcohol use during pregnancy could lead to the birth of an infant with deficient growth and mental development (US Cancer Statistics Working Group, 2003; Warner & Rosett, 1975). It was also commonly observed that some health problems "run in families," but until the discovery of DNA in the middle twentieth century, and the genomics revolution in later decades, the tools for investigating genetic causes of disease were limited. The discovery of molecular genetic methods of analysis subsequently revolutionized the understanding of human disease at the most fundamental level of cells and cellular processes, thereby opening the door to studies designed to uncover the ultimate causes of childhood health problems.

Fortuitously, the revolution in genomics coincided with the maturation of epidemiology as a research discipline. Epidemiology, the branch of health science concerned with identifying risk and protective factors and preventing diseases in populations, was quick to embrace the tools of modern genetics in addressing problems of child health and development. Unlike clinical medicine, which uses many of the same tools in the care

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of a single patient and family, epidemiology compares groups of people, hoping to identify factors related to the presence or absence of disease or health problems.

It is another fortuitous accident of history that, at the same time that genetics and epidemiology were developing, awareness of the special vulnerability of fetal development came to light. Before this time it was widely believed that the developing human fetus was largely invulnerable to disruption, especially from environmental factors other than alcohol. However, the twentieth century witnessed an unfortunate series of disastrous "epidemics" of birth defects that affected whole communities and vulnerable groups rather than isolated families, which had as their cause indisputably toxic prenatal environmental exposures. Examples include severe neurological impairments caused by the dumping of mercury into Minamata Bay, Japan (Koos & Longo, 1976; US Cancer Statistics Working Group, 2003), and birth defects caused by exposures of pregnant women to the medications thalidomide (Schardein, 1993; US Cancer Statistics Working Group, 2003) and isotretinoin (Lammer et al., 1985; US Cancer Statistics Working Group, 2003). These outbreaks of birth defects forever shattered the myth of the invulnerable fetus and ushered in a new era of research and a new discipline of teratology. Teratology is the study of the causes and biological processes associated with abnormal development and congenital malformations, including genetic and environmental causes of human birth defects and other health issues in child development.

As these new fields of research – genomics, epidemiology, and teratology – expanded and generated new knowledge of the causes of childhood health problems in the population, it soon became clear that, in the vast majority of individual children and their specific health conditions, neither genetic nor environmental causes alone could explain the majority of individual disease occurrences. Stated another way, a widespread view developed that genetic and environmental factors must in some way come together, or interact, to explain most cases of disease.

One way to conceptualize this idea is to consider how environmental exposures affect a person in light of his or her own unique genetic background, inherited from their biological parents. In this case, a person with a susceptible or vulnerable genetic background might be more likely to have an adverse health experience if he or she is exposed to a harmful environment, in comparison to someone with a resistant genetic background that protects the person in case of environmental exposure. Figure 1 illustrates this key concept, termed "gene–environment interaction."

In this chapter, we will further develop some key concepts of genomics, environment, and their interrelationships in child health and human development. We will discuss the ways in which epidemiology incorporates both genes and environment into the search for the causes of disease and how to prevent them from affecting growing children. These concepts will be illustrated with examples from neural tube defects (NTD) and childhood cancer. Finally, we will conclude by forecasting the impact of

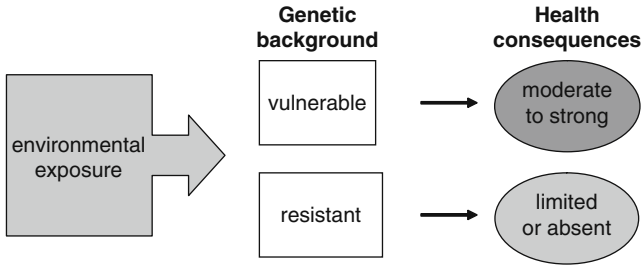

Figure 1. Interactions of genetic and environmental factors in human health problems. This figure illustrates the concept of "gene–environment interaction." If a person becomes exposed to a potentially harmful environmental factor, his health effect may depend on his genetic background. In the case of a susceptible background, such a person may experience health problems as a result of the exposure, in contrast to a genetically resistant person who was exposed to the same environmental factor but experiences little or no harm.

continued research and public health promotion resulting from applications in genomics and environmental health science to improve the human condition.

THE HUMAN GENOME PROJECT

The Human Genome Project (HGP) is an international effort, led by the United States' National Institutes of Health (NIH) and Department of Energy, to sequence and map all of the human genes. Deciphering all the three billion bases of the human genome will be an incredible resource that can help to identify the genes that can cause diseases in humans. Since the completion of the HGP in April 2003, molecular geneticists have been able to use the entire sequence of the human genome to identify and explore the biochemical, pharmacogenetic, and phenotypic consequences of human genetic variants, specifically those related to human disease including behavioral disorders. Even before its completion, the HGP identified its first gene, the gene for cystic fibrosis, through positional cloning in 1989 (Rannala, 2001; US Cancer Statistics Working Group, 2003). Through its progress, the completion of the HGP has provided the tools and high-throughput technology for genetic marker maps and physical mapping, DNA sequencing and cloning (both in vivo and in vitro), and gene identification (Slagboom & Meulenbelt, 2002; US Cancer Statistics Working Group, 2003). The HGP has improved the understanding of the molecular genetic basis of inherited and complex diseases such as diabetes, schizophrenia, and cancer (Sfar & Chouchane, 2008; US Cancer Statistics Working Group, 2003). In addition, in an effort to learn more about the interplay of genes and the role of biologically active regions of the genome in maintaining health or causing disease, the HGP has sequenced nearly 40 different species' genomes, ranging from *Caenorhabditis elegans* (*C. elegans*) and the opossum to the chimpanzee and orangutan (Kidd et al., 2008; US Cancer Statistics Working Group, 2003). Furthermore,

as part of the continued dedication to the HGP, researchers have completed 'sequence annotations' – the process of gathering all available information and relating it to the sequence assembly – of all human chromosomes (Gregory et al., 2006; Kidd et al., 2008; US Cancer Statistics Working Group, 2003). Through integrated clone-based mapping in multiple human genomes, researchers have been able to identify structural variation in the form of single nucleotide polymorphisms (SNPs), insertions, and deletions (Kidd et al., 2008; US Cancer Statistics Working Group, 2003). This clone-based framework provides a resource for recovery and integration of various forms of genetic variation in the study of disease association.

In addition to the discovery of the cystic fibrosis gene, researchers have also identified single genes associated with a number of other conditions, including Duchenne Muscular Dystrophy, myotonic dystrophy, neurofibromatosis, and retinoblastoma (Nwanguma, 2003; Suzuki et al., 2002; US Cancer Statistics Working Group, 2003). The number of identified human disease genes increased from 100 in 1990, when the HGP was started, to 1,400 in 2003 (Nwanguma, 2003; US Cancer Statistics Working Group, 2003). Furthermore, the HGP has helped catalyze the development of predictive tests of human diseases, as well as diagnostic tests that detect cancer and other health conditions earlier. Recently, scientists from the Cancer Genome Atlas project completed the first successful whole-genome sequencing of a cancer genome and its matched normal genome using tumor and skin samples from a deceased, female patient who had acute myeloid leukemia (AML) (Ley et al., 2008; US Cancer Statistics Working Group, 2003). This new mapping technology called 'massively parallel sequencing' represents a landmark achievement in identifying specific gene pathways or mutations associated with disease. The new genomic tools have revolutionized biology and medicine, and molecular geneticists have and will continue to utilize the tools developed through the HGP to identify, help in prevention of, and develop therapies for human diseases (Ley et al., 2008; US Cancer Statistics Working Group, 2003).

Several findings have led to the development of the hypothesis of "developmental origins of adult health and disease" suggesting that starting at conception, environmental factors, in particular maternal undernutrition, are instrumental in early life in programming of the risks for adverse health outcomes in adult life, such as cardiovascular disease, obesity, and the metabolic syndrome. Early physiological tradeoffs, including activation of the fetal hypothalamo-pituitary-adrenal axis (HPA axis), and the systems that maintain and regulate arterial blood pressure, confer an early fitness advantage such as fetal survival, while incurring delayed health costs (McMillen et al., 2008; US Cancer Statistics Working Group, 2003; Worthman & Kuzara, 2005).

A different field that is fast developing is epigenomics – the systematic genome-wide study of epigenetics, or the study of heritable changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence, such as DNA methylation, histone modifications, and RNA-mediated gene silencing (Clark, 2007; Peedicayil, 2008;

US Cancer Statistics Working Group, 2003). The National Institute of Health Roadmap Epigenomics Program is a trans-NIH effort that aims to understand the epigenetic processes that control genes during various stages of development (NIH, 2008). The central hypothesis of the NIH Roadmap Epigenomics Program is that the origins of health and susceptibility to disease are, in part, the result of epigenetic regulation of the genetic blueprint (NIH, 2008). The hypothesis predicts that epigenetic mechanisms that control stem cell differentiation and organ formation contribute to the biological emergence of disease (Peedicayil, 2008). Building on the knowledge of the human genome, the program aims to provide comprehensive reference epigenome maps as a tool for understanding and evaluating epigenetic regulation and how it relates to health and disease (NIH, 2008). The information generated by the NIH Roadmap Epigenomics Program is expected to provide an invaluable resource for researchers investigating the biological processes and management of a variety of human diseases (NIH, 2008; Peedicayil, 2006, 2008).

NEURAL TUBE DEFECTS

Neural tube defects (NTD) are brain and spinal cord birth defects. This is a group of heterogenous and complex congenital anomalies of the central nervous system (CNS), such as anencephaly, spina bifida, and encephaloceles. NTD are among the most common structural birth defects, surpassed in frequency only by congenital cardiovascular abnormalities. NTD such as anencephaly and spina bifida result from failure of neural tube closure during the early stages of embryonic development (Davies & Duran, 2003). Anencephaly is characterized by incomplete closure of the neural tube at the cranial end and subsequent loss of forebrain development. The defect usually causes stillbirth, or death shortly after birth. Failed closure at the caudal end of the developing neural tube results in spina bifida, typically a non-lethal condition, but often one that is accompanied by profound impairments. These two diseases affect 1 out of every 1,000 births in the United States (Stevenson et al., 2000).

In humans, the neural tube closes (neurulation) during the first trimester of pregnancy between the 17th and 30th post-fertilization days. This implies that the process is completed before many women may learn that they are pregnant. From a primary prevention standpoint, supplementation with folic acid prior to pregnancy has been demonstrated to reduce the risk of NTD (Czeizel & Dudas, 1992; US Food and Drug Administration, 2000). Folates are members of the vitamin B family involved in a large number of biochemical processes, particularly in the metabolism of homocysteine into methionine (Figure 2).

Homocysteine, an amino acid absent in normal diets, is essential for normal cellular growth, differentiation, and function. The reduction of active folate is the important regulator of homocysteine (Hcy) levels. Without active folate, hyperhomocysteinurea results, leading to a toxic state for cellular development and function. Excess homocysteine is associated with a variety of factors. These include genetic disorders

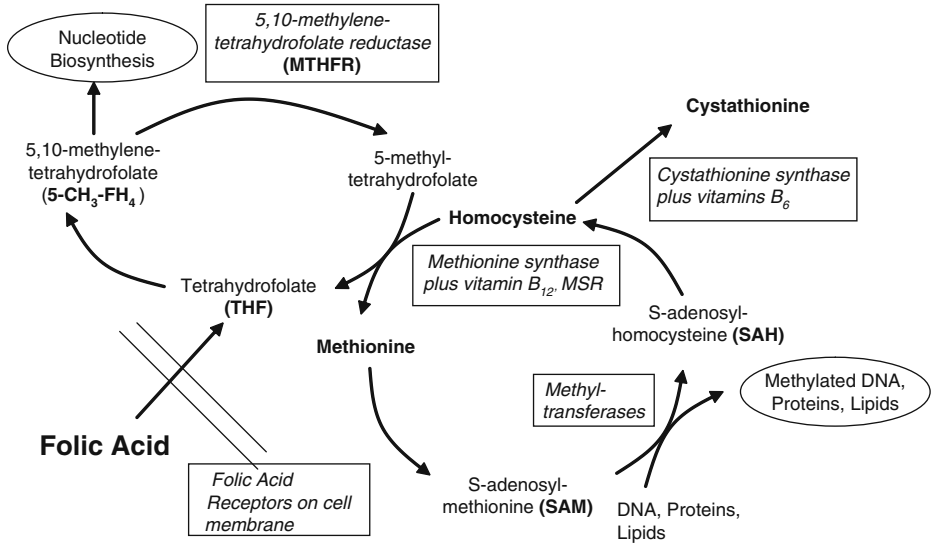

Figure 2. The folate–vitamin B12–methionine metabolic pathway.

(abnormalities of methionine–homocysteine metabolism), cardiovascular injury, and toxic effects on vascular endothelium and related disorders (Eldibany & Caprini, 2007). Deficiencies of vitamins B6, B12, and folic acid; a high meat diet; tobacco use; and other factors (D'Angelo et al., 2000; Ramakrishnan, Sulochana, Lakshmi, Selvi, & Angayarkanni, 2006). Hyperhomocysteinemia is also associated with pre-eclampsia, placental abruption, recurrent fetal loss, intrauterine growth restriction, intrauterine fetal death (Forges et al., 2007), NTD, congenital cardiac malformations, and diseases of premature atherosclerosis and venous thromboembolism, the so-called "cholesterol of XXI age" (Sztenc, 2004).

It has been shown that women who take medications known to be folic acid antagonists increase their risk of having an NTD-affected child by twofold. However, the remaining 30–50% of NTD cases that are not prevented by adequate folic acid intake are still unexplained. Mothers with normal levels of folic acid have given birth to NTD-affected children and exhibited relatively high levels of homocysteine. Researchers have suggested genetic variation in folic acid metabolism as a possible explanation.

The Etiology of NTD Involves Environmental and Genetic Factors

Despite years of intensive epidemiological, clinical, and experimental research, the exact etiology of NTD remains rather complex and poorly understood. It is thought that most NTD cases are multifactorial in origin, having a significant genetic component to their etiology that interacts with a number of environmental risk factors (Frey & Hauser, 2003; Volcik

et al., 2002). The development of the neural tube itself is a multi-step process strictly controlled by genes and modulated by a host of environmental factors. NTD are heterogenous in nature and in etiology; therefore the pathogenetic mechanisms of CNS anomalies may result from different target cell populations and different agents or exposures. NTD may also result from gene–gene interactions and/or gene–environment interactions, as explained below.

Genetic Causes of NTD

Compelling evidence for a genetic contribution to the causation of NTD is the observation that NTD show familial aggregation, even though they do not follow a strict classic, Mendelian pattern of genetic inheritance. For example, recurrence risk for NTD in siblings of patients with myelomeningocele is reported to range from 2 to 5% (Sebold et al., 2005). The incidence of NTD among first- and second-degree relatives of affected infants appears to be significantly higher than in the general population. In addition, females and monozygotic twins appear to be particularly prone to NTD (Windham & Sever, 1982). The prevalence of having both encephalocele and anencephaly is increased in multiple gestation births, whereas spina bifida is decreased in comparison to singletons, suggesting that multiples and singletons vary in their response to etiologic factors and that there may be separate factors that influence the development of each specific type of NTD. Animal studies indicate that there are as many as 100 genetic alterations affecting neurulation and almost all of them have homologs in humans (Juriloff & Harris, 2000; Klootwijk, Schijvenaars, Mariman, & Franke, 2004). Spina bifida occurs more frequently in autosomal trisomies.

Although NTD have been associated with several single gene disorders (for example, cerebrocostomandibular syndrome, Fraser syndrome, Meckel–Gruber syndrome, and Waardenburg syndrome), there is no single gene known to be solely responsible for NTD in humans. This is due, in part, to the paucity of families with several NTD-affected members, the fact that perinatal mortality and morbidity of individuals with NTD are profound, and with poor reproductive capabilities of affected survivors (Davidoff, Petrini, Damus, Russell, & Mattison, 2002; Fedrick & Adelstein, 1976).

Anencephaly has been reported to be more prevalent in certain communities with a high rate of consanguinity (Zlotogora, 1997), and spontaneous abortuses with NTD have a significant association with chromosomal aberrations, suggesting a genetic component to their etiology (Coerdt et al., 1997; Seller, 1995; Sepulveda et al., 2004) and providing additional evidence for a genetic basis for NTD. Furthermore, a significantly higher spontaneous abortion rate (48%) in the preceding pregnancy was found in a group of newborns with NTD group compared to a comparison group with other birth defects (20%) (Carmi, Gohar, Meizner, & Katz, 1994). Despite the declining prevalence rates of NTD in many parts of the world, there seems to be no decline in NTD recurrence within affected

families (Czeizel & Metneki, 1984; Papp et al., 1997), suggesting a strong genetic load in these affected individuals.

The recurrent risk for anencephaly in siblings ranges from 2 to 5%, much lower than the 25–50% expected under classic Mendelian recessive and dominant inheritance, respectively. However, there are some studies that report anencephaly involving autosomal recessive genes, with some environmental influence (Shaffer, Marazita, Bodurtha, Newlin, & Nance, 1990; Zlotogora, 1995). The timing and nature of such influence might explain why a significant number of recurrences involve a NTD phenotype that is different from the case phenotype. However, an autosomal dominant gene has been implicated in a familial aggregation of spina bifida occulta (Fineman et al., 1982). Further studies involving larger affected populations are required before some meaningful conclusions can be drawn on the heritability of open NTD.

As noted previously, twinning appears to be associated with a significant increase in NTD relative to the general population (Windham et al., 1982). An increased frequency of twinning is noted in the near relatives of those with upper level NTD. Conversely, NTD families with twins have a higher rate of NTD siblings than do families without twins (Garabedian & Fraser, 1994). Monozygotic twinning is more frequently concordant for congenital anomalies than dizygotic twinning (Windham et al., 1982). Some genetic as well as environmental factors are thought to make NTD families more susceptible to twinning, but this remains poorly understood (Garabedian & Fraser, 1994).

Interrelationship of Folic Acid and Genetics in NTD

Genetic studies of NTD have focused mainly on folate-related genes, based on the finding that folic acid supplementation prior to conception and perinatally reduces the risk of NTD. The metabolism of folate (folic acid's conjugate base) is an important process in the cell. Folate is both a methyl group donor and methyl group acceptor. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) plays an important role in the metabolism of folic acid. Specifically, MTHFR irreversibly reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MeTHF) (Jacques et al., 1996). The latter compound is an important cofactor involved in the conversion of homocysteine to methionine by methionine synthase. A reaction of methionine and ATP results in *S*-adenosylmethionine, which is the principle methyl group donor in cells (Figure 2). *S*-Adenosylmethionine is responsible for the methylation of DNA (regulating gene expression), proteins (important in post-translational modification), and lipids (important in their synthesis), meaning that the formation of *S*-adenosylmethionine from folate is critical for cell function. The loss of a methyl group from *S*-adenosylmethionine forms *S*-adenosylhomocysteine, which is a strong inhibitor of most methyltransferases.

During the metabolic cycle *S*-adenosylhomocysteine is then converted into homocysteine and adenosine. The resulting homocysteine is available for methylation by 5-MeTHF, which restarts the cycle. Insufficient

amounts of 5-MeTHF in the cell can lead to an accumulation of homocysteine. This, in turn, can tip the equilibrium of metabolites in favor of *S*-adenosylhomocysteine which can cause dysregulation of gene expression, protein function, and lipid and neurotransmitter metabolism.

Alterations in MTHFR may be responsible for some cases of NTD. The alteration occurs in DNA basepair 677 and is characterized by the substitution of a thymine (T) in place of the normal cytosine (C) nucleic acid. The resulting enzyme has decreased activity causing hyperhomocysteinemia. High levels of homocysteine in pregnant women have been associated with NTD-affected children. Meta-analytic studies of the link between the MTHFR 677C>T polymorphism and NTD have found that there is upwards of 60% excess risk for NTD when the mother is homozygous for the 677C>T variant (677TT) and a 10% excess risk for NTD when the mother is heterozygous for the 677C>T variant (677CT). Furthermore, the summary analysis described a 90% excess risk for NTD when the child is homozygous for the 677C>T variant (677TT) and a 30% excess risk for NTD when the child is heterozygous for the 677C>T variant (677CT).

A reduction in MTHFR activity by specific gene mutations (inducing hyperhomocysteinemia) has also been shown to be a risk factor for vascular thrombotic events, including coronary artery disease (Almawi, Ameen, Tamim, Finan, & Irani-Hakime, 2004; Graham et al., 1997). While several mutations within it were described, the best-characterized MTHFR gene polymorphisms are the C677T (Frosst et al., 1995) and the glutamate-to-alanine A1298C (van der Put et al., 1998) missense mutations. While both SNPs induce milder forms of MTHFR deficiency (Chango et al., 2000; Forrest, Horsley, Roberts, & Barrow, 1995), the A1298C SNP, located in the enzyme regulatory domain (unlike the C677T SNP which is found within the enzyme catalytic domain), does not result in either a thermolabile protein or increased total plasma Hcy (Friso et al., 2002; Hanson, Aras, Yang, & Tsai, 2001). Interestingly, 677CT/1298AC compound heterozygosity reportedly has similar clinical impact as C677T homozygosity (Chango et al., 2000; Chen, Xia, Rodriguez-Gueant, Bigard, & Gueant, 2005). Recent evidence suggests an association between the MTHFR SNP C677T and A1298C and head, neck, and lung cancer, as well as gastric cancer (Boccia et al., 2008; Boccia et al., 2009). These findings suggest that folate and methionine metabolism play important roles in carcinogenesis (Kamel, Moussa, Ebid, Bu, & Bhatia, 2007).

The "methylation hypothesis" is based on findings across numerous studies proposing a mechanism that explains the connection between folate, MTHFR, and NTDs. MTHFR provides methyl groups via *S*-adenosylmethionine to methylation reactions at the expense of purine and thymidine synthesis. Reduced MTHFR activity caused by the 677C>T polymorphism results in an altered distribution of methyl groups. This new distribution may result in insufficient methyl groups for DNA methyltransferase. Thus, there would be a reduction in DNA methylation, a condition that has been strongly suggested to result in disruption of the neurulation process.

Since the identification of this genetic risk factor of NTD, and the observation that elevated plasma Hcy levels are associated with NTD,

research has focused on genetic variations in the genes encoding for other enzymes in the folate and Hcy pathways and in folate transport and uptake. A few variants in these genes have been found to be significantly associated with an increased risk for NTD. However, the most common approach (a candidate gene approach) of investigating the genes involved in neurulation has failed to identify major causative genes in the etiology of NTD, and progress in understanding the genetic basis of NTD is based mainly on animal models. These have demonstrated an essential role for the planar cell polarity pathway (PCP) in mediating a morphogenetic process called convergent extension during neural tube formation. Alterations in members of this pathway lead to NTD in vertebrate models, representing novel and exciting candidates for human NTD (De Marco, Merello, Mascelli, & Capra, 2006; Kibar, Capra, & Gros, 2007).

Finally, methylenetetrahydrofolate dehydrogenase (MTHFD) is another enzyme which catalyzes the conversion of tetrahydrofolate to metabolites important for the de novo biosynthesis of purines and pyrimidines and thus DNA biosynthesis. There is some evidence for a role of the maternal genotypic MTHFD1 R653Q variant and abnormal neural tube development (Brody et al., 2002). This is an important observation that highlights not only the significance of folic acid-related genes, but also the influence of the maternal genotype on neural tube development. The variability in the data that can be produced ethnically, nutritionally, and in geographically different parts of the world (Hol et al., 1998) further illustrates the complexity of NTD etiology and may be explained by not only the genetic characteristics of the populations studied but also the differences in nutrition and environment.

Environmental Causes of Neural Tube Defects

The fact that the incidence rate of NTD (that is, the number of new cases occurring in a specified time period) is different depending on the geographic area, socioeconomic status of the parents, and season of the year, and the discordance noted above between observed and expected NTD rates in monozygotic twins, all point to the possibility that an environmental component is involved in the etiology of NTD. Studies on NTD provide some evidence that physical agents such as ionizing radiation, hyperthermia, drug compounds (e.g., thalidomide, folate antagonists, androgenic hormones, antiepileptics), substance abuse (e.g., alcohol), chemical agents (e.g., organic mercury, lead), maternal infections (e.g., rubella, cytomegalovirus, toxoplasmosis, syphilis), and maternal metabolic conditions (e.g., obesity, phenylketonuria, diabetes mellitus) are associated with congenital malformations of the CNS (Chang et al., 2003; Curtin et al., 2003; De Marco et al., 2006; Dietl, 2005; Dziadek, 1993; Fine, Horal, Chang, Fortin, & Loeken, 1999; Friedrich, 2002; Huang, Roelink, & McKnight, 2002; Loeken, 2005; Pani, Horal, & Loeken, 2002; Ray, Vermeulen, Meier, & Wyatt, 2004; Sever, 1995). Parental socioeconomic status, occupation, and possible occupational exposure to noxious agents, such as organic solvents, anesthetic agents, viruses, pesticides, paints or X-rays, have been reported to be associated with a higher risk

for NTD as well (Blanco et al., 2005; Sever, 1995; Shaw, Nelson, & Olshan, 2002). By design, all such studies should include women with spontaneous pregnancy loss, which is known to be associated with a high incidence of NTD. However, uniformity across studies has been lacking in the methods of assessment and misclassification of pregnancy outcomes, so that some potential cases may have been missed in some studies.

Maternal exposure to drinking water contaminated with carbon tetrachloride, trichloroethylene, and benzene has been reported to confer an increased risk of NTD and major cardiac defects (Bove et al., 1995). Other factors suggested to be associated with NTD include chronic inhalation of airborne chemicals from living in close proximity to their source (e.g., manufacturing plants handling polyvinyl chloride) (Theriault, Iturra, & Gingras, 1983) and toxic wastes from landfill sites located within 3 km of residence (Dolk et al., 1998; Marshall, Gensburg, Deres, Geary, & Cayo, 1997).

Elevated core body temperature (hyperthermia) can be harmful to developmental processes such as cell proliferation, migration, differentiation, and apoptosis. The response to increased heat appears to depend on the species, strain, embryonic developmental stage, dose, and duration of exposure (Edwards, Shiota, Smith, & Walsh, 1995; Edwards, Saunders, & Shiota, 2003). A similar dose–response relationship has not been established for human embryos. However, a recent meta-analysis suggests that maternal hyperthermia during gestation may be associated with an enhanced incidence of NTD (odds ratio 1.95) (Moretti, Bar-Oz, Fried, & Koren, 2005). Maternal exposure to very high external temperatures, such as in a sauna or hot water tub, during the critical period of neurulation has been found to increase the risk of NTD in offspring (Suarez, Felkner, & Hendricks, 2004).

Environmental, Dietary, and Genetic Interactions in NTD

Since NTD are multifactorial in origin, an understanding of the possible interactions of teratogens with susceptible genes is of particular interest. As in other areas of biology, animal models have an advantage here of being able to eliminate some of the confounding influences that would be inherent to human studies. Currently, there are over 100 mouse models of NTD. Most of these mice NTD phenotypically resemble human NTD (Harris, 2001). Among mouse and human homolog genes may be genes with alleles of partial function, which might coalesce to induce the risk of NTD. In this context, it needs to be understood that in addition to gene–gene interactions, there might also be instances where susceptible genes interact with teratogens thus enhancing the NTD risk (Finnell et al., 2004).

Seasonal or geographic variations often attributed to NTD incidence may result from gene–environment interactions. As an example, foods containing phytochemicals and herbal supplements may induce enzymes which could change the bioavailability of the active molecules in some drugs (Harris, Jang, & Tsunoda, 2003). Dietary modifications (such as drinking grapefruit juice) can alter the plasma concentrations of drugs.

Exposures to a drug considered safe in a given dosage for use in pregnancy in a given situation might reach teratogenic concentrations in some pregnant women due to ethnic and geographical differences.

There are also studies suggesting that polymorphisms in folate-metabolizing enzymes might be associated with an increase in meiotic non-disjunctions (O'Leary & Sheehy, 2002; Wong et al., 2002). Zinc (Zn) is a nutrient important for the functioning of some enzymes and transcription factors. A relationship between Zn and NTD was demonstrated experimentally (Warkany & Petering, 1972), and Zn-dependent transcription factors were shown to be risks for NTD in mouse models (Purandare et al., 2002). Zinc concentrations are also lower in mothers and children born with spina bifida (Groenen et al., 2003a; 2003b). The mechanism contributing to NTD in Zn deficiency in susceptible embryos is still unknown.

As mentioned, children affected with NTD and their biological parents who are heterozygous for MTHFR C677T mutation have low (but not deficient) plasma folate and elevated Hcy levels (van der Put et al., 1997a). Therefore, it has been proposed that in addition to low folate levels or polymorphisms in folate-metabolizing enzymes, lower vitamin B12 (cobalamin) concentrations during pregnancy may also independently contribute to an increased risk for NTD (Kirke et al., 1993).

Mothers of NTD-affected babies have been observed to have mildly elevated serum Hcy in response to methionine loading (Mills et al., 1995; Steegers-Theunissen et al., 1995). Methionine synthase reductase (MTRR) is required to maintain methylcobalamin (derived from vitamin B12) in an active state (Brody et al., 1999; Gulati, Brody, & Banerjee, 1999). In addition to vitamin B12, the remethylation of Hcy is dependent on transcobalamin (TC), methionine synthase (MTR), and MTR reductase (MTRR) (van der Put et al., 1997b). Mutations in these genes might be involved in elevation of total plasma homocysteine concentrations and in the causation of NTD. A strong association was found between polymorphisms in MTR 2756 AG/GG, TC 777 CG/GG/MTHFR 677 CC, and MTRR 66 GG/MTHFR 677 CC genotypes and increased risk for NTD in both Italy (Gueant et al., 2003) and the United States (Zhu et al., 2003). It can be concluded from the data that both independent genetic effects and gene–gene interaction may play a role in NTD risk. Further studies and multilocus, rather than single locus, analyses might provide deeper insights into the genetic susceptibility to NTD.

CHILDHOOD CANCER

A wide range of organs and tissues can give rise to malignancies, or cancer, in children. As might be expected, there are specific risk factors for each type of childhood cancer. Childhood leukemia represents 31% of all cancer cases occurring among children younger than 15 years of age (US Cancer Statistics Working Group, 2003, 2006). Of all the types of childhood leukemia, 79% of the cases have acute lymphoblastic leukemia

(ALL) (Linabery & Ross, 2008; Simpson, Smith, Ansell, & Roman, 2007). ALL is a progressive, malignant disease characterized by large numbers of immature white blood cells that resemble lymphoblasts. The malignant transformation of marrow lymphocytes is followed by their multiplication and accumulation in the marrow as leukemic lymphoblasts, resulting in the insufficient production of other blood cells such as erythrocytes (red blood cells), leukocytes (white blood cells), and platelets. ALL has an annual incidence rate of 43 cases per million in the United States (US Cancer Statistics Working Group, 2003; Ries et al., 1999; Linabery & Ross, 2008). ALL also occurs in adults, where it accounts for 20% of all adult leukemias.

The Etiology of Childhood Leukemia Involves Environmental and Genetic Factors

Despite a rising incidence rate over the past few decades, the risk factors for childhood ALL are largely unknown. In utero exposure to diagnostic X-rays is one of the only known causes of childhood ALL; however, due to the extremely low number of individuals exposed, this factor can explain only a small fraction of cases occurring in the general population (Ross, Davies, Potter, & Robison, 1994). Other factors that have been associated with childhood leukemia include maternal history of fetal loss, high infant birth weight, and parental and child pesticide exposure. Other studies have observed a 10- to 20-fold increased risk of leukemia in children with Down syndrome (Robison, 1992; Ross, Spector, Robison, & Olshan, 2005) – a vexing circumstance for which the molecular or biochemical basis of the association remains illusive (Alderton et al., 2006). Taken together, all of these factors explain less than 10% of childhood leukemia incidence (Greaves & Alexander, 1993). Since the cause of most ALL cases is unknown, prevention still lags behind (Linet, Ries, Smith, Tarone, & Devesa, 1999). As in other childhood and adult cancers and chronic diseases, many have surmised that ALL is most likely multifactorial, involving an interaction between the environmental and human genetics (Aydin-Sayitoglu, Hatirnaz, Erensoy, & Ozbek, 2006; Chokkalingam & Buffler, 2008).

Genetic Causes of Childhood Leukemia

Families with multiple children affected by ALL are quite rare, occurring less than 5% of the time. This does not imply that genetic factors are absent; on the contrary, the currently accepted model for how ALL develops is based very strongly on genetic changes that have been observed among affected children (Linabery & Ross, 2008). According to this model (Greaves, 2004), studies of ALL in identical twins, studies using newborn blood spots, and studies of umbilical cord blood have shown that chromosomal translocations responsible for initiating the cancer process originate during prenatal life. Later on (i.e., shortly after birth or late in

gestation), additional genetic changes occur, probably stimulated by environmental factors, which complete the cascade of events causing this type of leukemia to develop. ALL, therefore, may be viewed as a prototypic example of gene–environment interaction, similar to the example we have already discussed above in NTD, and which we will revisit below in the context of ALL and the environment (Dorak, McNally, & Parker, 2007).

In ALL, particularly among affected infants and less so among older children, there are complex interactions between genes that appear to be critical in the initiation of the cancer. The MLL gene, for example, "partners" with more than 50 other genes to form pairs of abnormal recombinations, and many of these genes have yet to be adequately described and characterized (Greaves, 2004; Tauchi et al., 2008). The genes TEL and AML1 are found combined or "fused" together in many cases of infant ALL, but they are also found in combination with other genes, and the gene products of such fusions can alter the normal development and function of the blood cells (Greaves, 1999; Lin et al., 2008). As recent progress in this field, aided by evolving genetic technologies, has shown that the origin of these fusion genes lies in the initial breakage of the double-stranded DNA during fetal development, the question arises: "What is causing these double strand breaks?" This is an important area for future research.

Environmental Factors and Childhood Leukemia

Some have hypothesized that a potential explanation for the increasing incidence rate of ALL in developed countries is pesticide exposure (Infante-Rivard & Weichenthal, 2007; Menegaux et al., 2006; Rudant et al., 2007). Pesticides are ubiquitous in the environment and 85% of households in the United States store at least one pesticide for home use (Adgate et al., 2001). Certain classes of pesticides, such as organophosphates (OP), are highly active biologically. The EPA has recognized that OP require close regulation and monitoring for human health effects. This is exemplified by the phaseout of chlorpyrifos in 2001 from the consumer market due to the special risk that it posed for children. Although there is growing evidence in support of an association between pesticide exposure and childhood leukemia, it is limited by ecological study designs (where exposures are inferred from data on area-wide exposures rather than information on personal level exposures), reliance on self-reported exposures from parents, and lack of biological measurements (Buckley et al., 1989; Infante-Rivard, Labuda, Krajinovic, & Sinnett, 1999; Lafiura et al., 2007; Leiss & Savitz, 1995; Meinert et al., 1996; Meinert, Kaletsch, Kaatsch, Schuz, & Michaelis, 1999; Meinert, Schuz, Kaletsch, Kaatsch, & Michaelis, 2000). Elevated risk has consistently been associated with no-pest strips and home use of pesticides (Buckley et al., 1989; Infante-Rivard et al., 1999; Leiss & Savitz, 1995; Lowengart et al., 1987; Ma et al., 2002), but associations with garden pesticide use have been mixed. While several large studies in California found little evidence of an association between agricultural pesticide use and childhood leukemia (Infante-Rivard et al., 1999; Leiss et al., 1995; Buckley et al., 1989; Lowengart et al.,

1987; Ma et al., 2002; Reynolds et al., 2002, 2005), these results are in contrast with the associations observed with household exposures to pesticides. The association may depend on several factors including the timing of exposure, type of agent, dose, chronicity, and pathway of exposure (Merhi et al., 2007). Furthermore, some persons may be more susceptible to the effects of specific pesticides due to inherited mutations in their detoxification pathways which may result in adverse outcomes.

Part of the challenge in studying childhood cancer and pesticides is that pesticides, as broadly defined by the United States Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), are a wide array of chemicals or mixtures of chemicals intended to prevent, destroy, repel, or mitigate any pest, including insects, rodents, fungi, and weeds (Laws & Hayes, 1991). The contemporary pesticides in commercial and consumer uses include organophosphates, carbamates, triazines, synthetic pyrethroids, and others. Unfortunately, because of the heavy agricultural use of these chemicals, humans are continually exposed to many of these chemicals via the food chain and also through residential use (Peiris-John & Wickremasinghe, 2008). Other common exposure sources for children include treated areas in the home and yard and treated pets. Agricultural pesticides may expose children inadvertently via spray drift or farm work.

OP are one of the main classes of insecticides, in use since the mid-1940s. OP can exert significant adverse effects in non-target species including humans. Currently debated and investigated issues in the toxicology of OP are the possible long-term effects of chronic, low-level exposures, genetic susceptibility to OP and developmental toxicities. Experimental studies in rodents indicate that pre- or postnatal exposure to chlorpyrifos (formerly in widespread use in homes and gardens) affects various cellular processes (e.g., DNA replication, neuronal survival, glial cell proliferation) and non-cholinergic biochemical pathways (e.g., serotoninergic synaptic functions, the adenylate cyclase system) and causes various behavioral abnormalities (Aldridge, Seidler, Meyer, Thillai, & Slotkin, 2003; Dam, Seidler, & Slotkin, 1998; Dam, Seidler, & Slotkin, 2000; Garcia, Seidler, & Slotkin, 2003; Jett, Navoa, Beckles, & McLemore, 2001; Lee et al., 2004; Ricceri et al., 2003; Roy, Sharma, Seidler, & Slotkin, 2005; Slotkin, Seidler, & Fumagalli, 2008; Song et al., 1997). In vitro studies have shown OP to inhibit astroglial cell proliferation and to cause neuronal apoptotic death (Caughlan, Newhouse, Namgung, & Xia, 2004; Guizzetti, Pathak, Giordano, & Costa, 2005; Howard et al., 2005; Qiao, Seidler, & Slotkin, 2001). These findings, together with biomonitoring study outcomes that indicate OP exposure in children, particularly in inner cities and in farming communities (Landrigan et al., 1999; Lu, Kedan, Fisker-Andersen, Kissel, & Fenske, 2004), have led to regulatory restrictions on the use of certain OP and heightened concerns for their potential neurotoxic and secondary harmful effects in children (Eskenazi, Bradman, & Castorina, 1999; Garry, 2004; Tilson, 2000; Weiss, Amler,& Amler, 2004).

Children have a number of unique characteristics which may increase their risks from and of exposure to pesticides and other environmental pollutants. Again, vulnerability is greatest during fetal development, and at

the time in which the brain, bone marrow, and other organs are subject to environmental influences during their formation, with specific organ systems having critical windows of extreme susceptibility (Dorak et al., 2007; Lafiura et al., 2007; Mallol-Mesnard et al., 2007; Roman et al., 2007). Children's exposure to pesticides may be greater than adults' because their skin is more permeable, and because their livers do not excrete as efficiently as those of adults. Also, as newborns they have lower levels of the OP detoxification enzyme paraoxonase-1 (PON-1) (Chen, Kumar, Chan, Berkowitz, & Wetmur, 2003; Karmaus, DeKoning, Kruse, Witten, & Osius, 2001; Mueller et al., 1983). Their chance of ingestion is increased due to hand-to-mouth behavior, and their dermal contact is increased because of a proportionally larger skin surface-to-mass ratio. Parents may inadvertently expose their children to pesticides by tracking pesticides indoors on their shoes or on their clothing or bodies from exposures at work. Some pesticides that degrade outdoors in sunlight are more persistent once they are present indoors. Children also have a longer life expectancy in which to develop diseases with long latency periods (Dorak et al., 2007; Roman et al., 2007).

The role of pesticides in ALL and other cancers has been hypothesized but is not especially well understood at present (IARC, 1991; Zahm & Ward, 1998). The mechanism of acute toxicity is known for many pesticides, and there are some studies of chronically exposed workers, but little is known about the long-term effects of chronic, low-dose exposure, particularly among children and women during early gestation. A systematic review of the scientific literature (1990–2003) on human health effects of commonly used pesticides concluded that common pesticides are associated with fetal birth defects, neurological damage and cancers, and that children are especially vulnerable (Lafiura et al., 2007; Sanborn et al., 2004).

Environmental and Genetic Interactions in Childhood Leukemia

Individual responses to environmental toxicants are influenced by the metabolic capability of the individual, which in turn is under the control of the genes that code for certain metabolic enzymes. Inheritance of variants in key metabolizing genes may alter the pharmacokinetics and thus the biological and health outcomes resulting from exposure to pesticides (gene–environment interactions). Inheritance of mutated genes has been shown to be involved with increased activation and/or decreased detoxification/elimination of environmental mutagens and to be associated with serious disease outcome (Strange, Lear, & Fryer, 1998). An important focus of this research is the concept of genetic susceptibility (see Figure 1) (Chokkalingam & Buffler, 2008). An advantage of studying genetic associations is that they are highly measurable and are not prone to recall bias.

The enzymes PON1, GSTM1, GSTT1, GSTP1, and CYP2E1 are examples of important genetically based mediators involved in the biotransformation and detoxification of a variety of xenobiotics present in food, occupational chemicals, tobacco smoke, drugs, pollutants, and pesticides

(Aydin-Sayitoglu et al., 2006; Furlong et al., 2005; Guha et al., 2008; Urayama et al., 2007). Many chemicals undergo metabolism mediated by these genes, and often there are reactive oxygen species (ROS) produced as a result of the metabolism. If levels of ROS in the cells are high then cellular damage may occur, but fortunately some of these genes act to produce enzymes capable of detoxifying the ROS, as seen in Figure 2 (Chow et al., 2008; Jantova, Repicky, Letasiova, & Cipak, 2008; Shin et al., 2009).

Polymorphisms (normal variations in DNA) in the genes coding for these enzymes have been associated with increased susceptibility to different cancers, including hematological (blood cell) malignancies (Aydin-Sayitoglu et al., 2006; Guha et al., 2008). Some studies imply that genetic variants of xenobiotic-metabolizing genes influence the risk of developing childhood ALL; for example, low NQO1 activity caused by a heritable mutation in this gene has been associated with increased risk for childhood ALL (Smith et al., 2002), while another study suggested that GSTM1 and GSTT1 genotypes may play a role in the risk for childhood ALL in some populations (Chen et al., 1997).

The PON1 gene possesses several polymorphisms that affect the efficiency of the enzyme in metabolizing different compounds (the Q192R polymorphism) and its level of expression in cells (the C-108T polymorphism) (Costa, Cole, & Furlong, 2003; Costa, Cole, Vitalone, & Furlong, 2005). Extensive research in transgenic animal models clearly indicates that PON1 "status," encompassing both the Q192R polymorphism and the level of PON expression, plays a highly relevant role in modulating the acute toxicity of some OP (Li et al., 2000). PON1 activity is lower in newborn infants than older children and adults, which implies that they have a reduced capacity to detoxify OP (Chen et al., 2003). In addition, there is a larger difference in activity between genotype groups in neonates than in adults (Chen et al., 2003) (Figure 3).

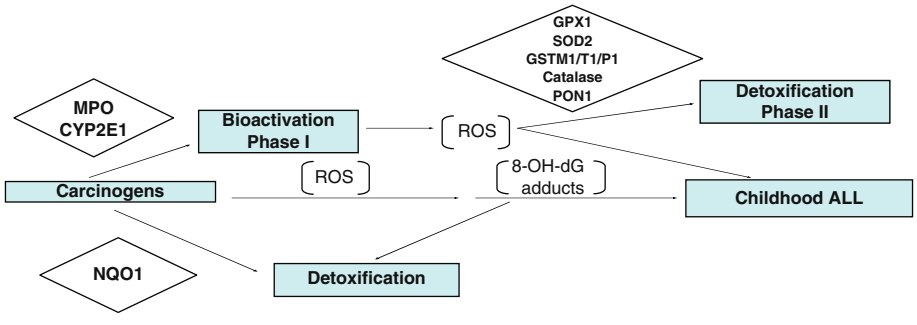

Figure 3. Biotransformation pathways and role of candidate genes in cancer risk. ROS (reactive oxygen species) in this figure refers to partial reduction products of oxygen such as superoxide anions ($O_2^{\bullet -}$), hydroxyl radicals ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2), which can result from the metabolism of carcinogens. These radicals can lead to a variety of types of DNA damage, including DNA adducts (8-OH-dG), mutations, and chromosomal aberrations (Bird, Draper, & Basrur, 1982). *Diamond shapes* in this figure refer to genes that mediate each step in the biotransformation of carcinogens: paraoxonase (PON1), cytochrome P450 2E1 (CYP2E1), superoxide dismutase (SOD), catalase, mitochondrial glutathione peroxidase (GPX), NAD(P)H quinone oxidoreductase gene (NQO1), myeloperoxidase (MPO), glutathione-*S*-transferase (GST) types M1 and T1.

Several examples of studies that assessed gene–environment interactions in ALL have been published. Maternal exposures to household pesticides, solvents, and other hazardous chemicals were significantly associated with excess risk of MLL gene rearrangements, which are observed in approximately 80% of childhood ALL cases (Alexander et al., 2001; Pombo-de-Oliveira & Koifman, 2006; Pui, Relling, & Downing, 2004; Pui, 2004), probably originating in utero, during the fetal development of the blood cells (hematopoiesis) (Greaves, 2005). Another study showed GSTP1 Val allele carriers were at a higher risk for ALL (Canalle, Burim, Tone, & Takahashi, 2004), and when the mutant CYP1A1 and CYP2E1 alleles were considered together with the GSTM1 and GSTP1 risk-elevating genotypes, the risk of ALL was increased further (odds ratio = 10.3), suggesting a combined effect (Chen et al., 2008; Gallegos-Arreola et al., 2008; Gra et al., 2008). Thus, it is plausible that exposures to xenobiotics interact with the genetic variation in these enzymes to play a role in the causal pathway of childhood ALL (Kang et al., 2008; Stanulla et al., 2005).

Although this chapter focused on gene–environment interactions, DNA repair genes have also been associated with both increased risk of and protective effects against childhood ALL. Individuals with a genetically programmed robust response to DNA damage may be protected from exposures to DNA-damaging agents, while those with genetically impaired DNA repair pathways may be at increased risk for health effects (Sharma & Odenike, 2008). For example, it has been shown that individuals with haplotype C of the X-ray repair cross-complementing group 1 (XRCC1 194-Arg-280Arg-399Gln) had an increased risk for childhood ALL, while haplotype B (194-280Arg-399Arg) had a decreased risk (Pakakasama et al., 2007).

CONCLUSIONS: IMPACTS OF EXPANDING RESEARCH IN GENOMICS AND CHILDREN'S HEALTH

Advancing our understanding of the genetic causes of many childhood health problems lies not only in the evolution and progress of genetics itself, but also in the fuller understanding of how a person's genetic background influences how he or she biologically responds to challenges confronted in the environment. For the field to progress further, epidemiological studies of the type we have reviewed (sometimes called molecular epidemiology in recognition of the use of molecular tools in traditional study designs) must continue to flourish and to tackle increasingly complex questions on how acute and chronic diseases arise within individuals and families. Therefore, a transdisciplinary approach will be needed more than ever, wherein experts from a wide range of biomedical and behavioral fields work together on a common research goal. As such work yields new understandings of how genomics affects the family, the prevention and control of health problems will also flourish in response to new knowledge of how to strengthen the body's innate capacity to heal itself before the disease becomes manifested.

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2

Psychological Genetics: Understanding the Nature of Psychological Differences Through Etiology

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INTRODUCTION

Questions about the roles of nature and nurture in human behavior have changed radically over time. Arguments about whether genes or environment play a role in human behavior have largely been resolved, with a well-documented role for both factors in the development of psychological and behavioral traits. Correspondingly, the nature of inquiry about genetic influences has changed, to instead focus on how genes exert their influences, with regard to the specific genes involved, the biological processes underlying their expression, and the environmental and psychological factors initiating these processes.

Interestingly, this increased focus on how genes influence behavior has also paralleled a change in the way in which behavioral genetic inquiry informs psychological and behavioral theory. Whereas genetic and environmental factors were once primarily invoked as causal explanations for predefined psychological phenotypes (i.e., psychological characteristics of interest), increasingly they are being invoked to help define the phenotypes themselves. In this way, genetic and environmental factors are not only used to answer questions about *why* a behavior occurs, but also to help understand *what it is*.

The current chapter has three primary purposes to (1) explain fundamental elements of behavioral genetic design and analysis, (2) review general patterns of observations in behavioral genetics, and (3) discuss

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how these observations have influenced subsequent thinking about the relationships between genes and behavior. Human behavioral genetic designs, necessarily observational in nature, are the focus of this chapter. It is important to note that there are many important animal models, experimental as well as observational, that greatly inform psychological theory but these will not be discussed herein.

PRINCIPLES OF BEHAVIORAL GENETIC DESIGN: THE COINHERITANCE OF GENETIC AND PSYCHOLOGICAL CHARACTERISTICS

The primary assumption underlying nearly all behavioral genetic study designs, regardless of the level of analysis, is that psychological features are coinherited with genetic features. Designs vary in the way that "genetic feature," "coinheritance," and "psychological feature" are defined, but the basic principle is the same. To the extent that two individuals inherit the same genetic features, they will be relatively similar in some psychological features, and to the extent they inherit different genetic features, they will be relatively different in those psychological features.

Approaches to defining genetic features. One major way in which behavioral genetic study designs differ is in how genetic features are defined. An important distinction can be made between designs that assume genetic features are completely observed or directly measured and designs that assume genetic features are unobserved or indirectly measured.

In many molecular genetic studies of behavior, for example, individuals are genotyped on some locus – that is, their genetic sequence is determined for some location in the genome and the feature of interest is the polymorphism – the normal variation in genetic sequence at that locus and how it is related to behavior. The sequence for each individual is assumed to be known and directly observed.

In other cases, however, the genetic feature of interest is assumed to be unknown or cannot be directly observed. In cases where the genetic features are unobserved, knowledge about them is inferred from known biological relationships. For example, in studies of monozygotic (i.e., identical) twins, the genetic features of interest – the actual genotypes of the twins – are unknown and unobserved. However, based on current understanding of twinning, it is known that such pairs of twins share identical genotypes, and this knowledge can be used to study relationships between the genetic features of interest and behavior.

Similarly, in some linkage studies, the genetic features of interest are not directly observed, but are inferred from what is known about chromosomal recombination. In such studies, data on a limited number of genes are used to make inferences about many nearby genes, based on the notion that genes nearer to each other on a chromosome tend to be inherited together. Although the genes of interest are never actually observed, information about them can be gained from the genes that are observable.

Approaches to defining coinheritance. Another major way in which behavioral genetic designs differ is in how they approach coinheritance of genetic and psychological features. There are two primary types of designs in this regard: (1) those in which coinheritance of genetic and psychological features is examined within families (within-family designs) and (2) those in which coinheritance of genetic and psychological features is examined independent of or across different families (between-family designs).

In within-family designs, coinheritance of genetic and psychological features is generally examined by determining the extent to which psychological features correlate across relatives as a function of how similar they are in some genetic feature. For example, given their degree of genetic relatedness, one might expect the correlation between monozygotic twins in some psychological feature, such as anxiety, to be twice that of dizygotic (i.e., fraternal) twins, and the correlation of the latter to be approximately equal to that of biological parents and their offspring. Similarly, biological siblings differing in the number of alleles (i.e., versions of a gene) they have in common at some locus might be compared in how correlated they are in levels of some psychological characteristic. As the degree of genetic relatedness increases, the correlation between relatives on some feature is expected to increase.

In between-family designs, or those designs ignoring family structure, the presence or absence of some genetic feature is simply correlated with the psychological feature, independent of family structure. Unrelated individuals differing in some polymorphism might be statistically compared in their levels of some behavioral feature, such as anxiety, to determine whether different forms of an allele are associated with different probabilities of having that feature.

Within and between-family designs differ in their advantages and disadvantages. By examining the coinheritance of behavioral and genetic features within families, environmental and other effects that influence all members of a family, but differ between families, can be controlled to some extent. A common example of this is sociodemographic influences associated with ethnic background: if family structure is ignored, an association between an allele and some psychological characteristic can be confounded with a sociodemographic effect if the frequency of that allele differs among individuals with different ethnic and sociodemographic backgrounds. When allele frequencies differ among sociodemographic groups – a phenomenon known as *population stratification* – it can be difficult to determine whether differences between individuals are due to differences in a specific allele, other genetic differences, or differences in environmental circumstances. However, if it can be shown that the association occurs within families, among individuals who share the same backgrounds, then these concerns might be mitigated (Fulker, Cherny, Sham, & Hewitt, 1999; Laird & Lange, 2006).

In general, within-family designs allow for more precise modeling of environmental as well as genetic effects. Recruiting families, however, requires significantly greater resources than does recruiting unrelated individuals, which often results in smaller sample sizes and potentially

reduced statistical power. Finding an appropriate balance between gains and losses in statistical power due to detailed family information versus sample size can oftentimes be critical to study design and is challenging.

Approaches to defining psychological features. Finally, study designs differ in the ways that they define phenotypes of interest. A psychological construct such as intelligence or negative emotion, for example, might be measured as a continuous variable, where individuals differ gradually in their standing, from low to moderate to high, with intermediate values throughout. Alternatively, a construct may be measured discretely, such as in the case of binary presence or absence of a psychiatric diagnosis. Psychological features of interest may reflect individuals' standing on some variable at a particular point in time, as in cognitive capacity at a particular age, or reflect patterns of change over time, such as in developmental patterns of change.

Differences in definitions of phenotypes have important implications for interpretation of behavioral genetic observations. For example, many forms of psychopathology are continuously rather than discretely distributed (e.g., there are degrees of psychopathology rather than presence or absence thereof) (see Markon & Krueger, 2005, for details). Inappropriately discretizing a variable into groups may decrease power to detect genetic effects compared to a design in which the variable is left as continuous. Similarly, if some psychological features of interest are closely related and share some etiology, combining them may increase power to detect common genetic influences. For example, evidence suggests that different forms of substance use share a common etiology, that is in turn shared with personality characteristics such as impulsivity (Krueger & Markon, 2006); examining these different forms of psychopathology with respect to a single liability (as a form of *pleiotropy*) may increase power to detect genetic effects (Dick et al., 2008; Stallings et al., 2005).

TYPES OF BEHAVIORAL GENETIC DESIGNS

Arguably, there are almost as many variations on behavioral genetic study designs as there are behavioral genetic studies themselves. Most designs can be classified broadly as one of three types: (1) a family, twin, or adoption design, (2) a linkage design, or (3) an association design. These designs are sometimes combined, as might be the case in a family association study, or a combined linkage and association study, but can be distinguished conceptually. These designs are reviewed below.

Family, twin, and adoption designs. Despite differences in their family structures, these designs all adopt the basic within-family approach outlined above. By including individuals within a family who vary in their degree of genetic relatedness, the effect of genetic similarity on behavioral similarity can be examined. A design might compare parent–offspring and grandparent–offspring correlations, monozygotic and dizygotic twin pair correlations, or adoptive sibling and biological sibling correlations to determine how the degree of genetic relatedness is related to behavioral similarity. Oftentimes, elements of family, twin, and adoption studies are

combined, for example, twin–family studies including families with twins and families of twins (e.g., D'Onofrio et al., 2007), family–adoption studies including families with adopted children, or twin–adoption studies, such as those in which twins are reared apart.

The basic rationale of family, twin, and adoption studies is illustrated in Figure 1. The correlation between a psychological feature P_1 in one relative and P_2 in another relative is modeled in terms of the relatives' similarity in genetic and environmental backgrounds. G_1 and G_2 represent the genotypes of the relatives; *g* represents the correlation or relationship between these genotypes in terms of percent of genes shared. For example, for monozygotic twin pairs, $g = 1$; for dizygotic twin pairs, sibling pairs, or parent–offspring pairs, $g = 0.5$; for adoptive children and their parents, $g = 0$. C_1 and C_2 represent the family backgrounds of the relatives. For individuals in the same family, the correlation *c* between C_1 and C_2 is 1, because they share the same family environment; for individuals in different families, this correlation would be 0, because their family environments are unshared. E_1 and E_2 represent those environmental factors that are not shared between relatives, including random effects that occur for one relative but not another, as well as measurement error. Because these random effects (i.e., nonshared environmental factors) are assumed to affect one relative but not another, they are assumed to be uncorrelated – the correlation between E_1 and E_2, not shown, is assumed to be zero (note that for individuals raised in different families, the family environments, C_1 and C_2, effectively become nonshared environments).

In the presence of purely genetic effects, one would expect monozygotic twins to be perfectly correlated in some psychological feature, such as anxiety or cognitive ability. Similarly, the observed correlation would be half that in dizygotic twins and zero in adoptive siblings. In the presence of

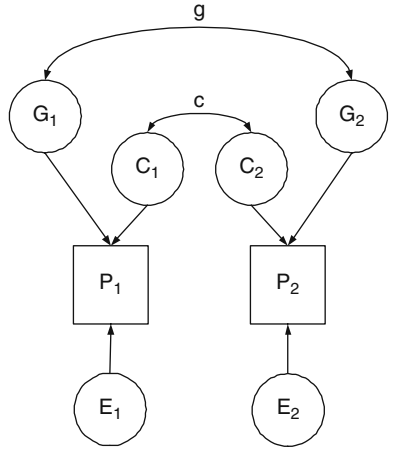

Figure 1. Standard model for genetic and environmental relationships between relatives. *G*, *C*, and *E* represent genetic, family environmental, and nonshared environmental factors, respectively; *P* represents phenotypes; *subscripts* indicate in which relative these occur; *g* and *c* indicate degree of relationship between genetic and family environmental factors across the relatives.

random environmental influences on one family member that do not affect another (E in Figure 1), one would expect the correlation between monozygotic twins to be less than perfect, because the lack of correlation in these effects across twins would decrease the observed correlation in the psychological feature. In the presence of environmental influences that affect all members of a family (C in Figure 1), one would expect the correlation between adoptive siblings to be greater than zero, because they share this influence.

Linkage studies. Linkage studies in many ways represent an extension of family and twin designs to the level of genomic regions rather than the entire genotype. Because genes that are physically close to one another on the chromosome are more likely to be inherited together during recombination, a relatively small set of genes can be used to estimate the genetic similarity of two relatives at a particular point on the chromosome. Just as family designs model psychological similarity as a function of genetic similarity across the genome, linkage designs model psychological similarity as a function of genetic similarity in a particular genomic region.

In this regard, Figure 1 can also be used to illustrate the rationale of linkage analysis. In linkage analysis, the genetic correlation g between G_1 and G_2 refers not to a genomewide genetic correlation, but the genetic correlation in a particular genomic region, such as a particular area of a particular chromosome. The genetic correlation g for a particular region is estimated based on patterns of similarity across a limited number of gene markers in the region. In the presence of effects of that genomic region, one would expect the observed correlation in some psychological feature to increase as the genetic correlation g between relatives in that region increases. By examining many such regions across the genome, one can delineate the different effects of particular genomic regions on variation in a particular psychological feature.

Biological siblings, for example, share half of their genes on average across the genome, in the sense that they inherit half of their genes from the same biological parent on average. In this sense, the average genomewide $g = 0.5$; however, at any given location on a chromosome, their genetic similarity might be more or less than that average. They might be identical in their genetic sequence at a specific location, with identical alleles and $g = 1$; their genetic sequence may be unrelated to one another at that location, with the different siblings inheriting different genetic material at that location, in which case $g = 0$; or they may be intermediate in their level of genetic similarity, inheriting one allele from the same parent, and another from different parents, in which case $g = 0.5$. If some gene in that region of the chromosome has significant effect on a particular psychological trait, one would expect siblings who inherit the same genetic material in that region to be more highly correlated in that trait than siblings who inherit different genetic material in that region.

Association studies. The rationale of association analysis is arguably somewhat intuitive: individuals differing in their polymorphisms at a particular locus are compared in some psychological feature to determine whether that gene influences behavior. One might attempt to determine, for example, whether having a certain polymorphism increases the

probability of a psychological feature of interest. In contrast to family and linkage studies, individuals need not be related: all that is required is sample variation in the polymorphisms and psychological features of interest. Meta-analyses have concluded, for example, that the 7-repeat allele of the dopamine D4 receptor (DRD4) gene is more likely to be observed among those with attention-deficit/hyperactivity disorder (ADHD) than in controls (Faraone, Doyle, Mick, & Biederman, 2001; Li, Sham, Owen, & He, 2006).

Advantages and disadvantages of designs. Each of these types of designs has advantages and disadvantages, which are continually changing due to modifications in technology and the ways in which the designs are applied. Although family, twin, and adoption designs cannot address questions about the influence of specific genes or genomic regions, for example, they are well suited to address questions about general processes through which genetic and environmental influences are mediated psychologically and behaviorally. Such designs are arguably unparalleled in their ability to address questions about specific environmental influences and the complex interplay between genes and environment, broadly speaking, during human development.

Linkage analyses occupy somewhat of an intermediate position between family and association studies in their advantages and disadvantages. Although they do not generally provide detailed information about the influence of a particular gene, for example, they do provide more detailed information about the nature of genetic influences, in terms of physical location in the genome, than do family studies, and generally do so over a wider range of the genome than association studies. Moreover, by adopting a within-family approach, linkage analysis avoids some of the ethnic or population stratification confounds that challenge association studies, as described above.

Association studies provide the most detailed information about the effects of a particular genomic region or polymorphism. Various works suggest that association studies provide greater statistical power to detect particular genetic effects than linkage analysis, especially as the level of precision allowed by genetic sequencing continues to increase (Risch & Merikangas, 1996). Whereas family, twin, and adoption designs broadly characterize processes by which genetic influences are manifested, and linkage designs more precisely characterize the physical location of these influences, association analysis ultimately establishes a link between a particular psychological feature and a specific polymorphism or other type of genetic feature of interest.

It is important to note that in practice, many top-quality studies combine features of all three types of designs simultaneously and that distinctions between designs can become blurred. The distinction between linkage and association analysis is sometimes unclear, for example (Ott, 1989), and both methods can be employed in a family design (Laird & Lange, 2006). A twin–family or family–adoption study, in which individuals are sequenced at many loci across the genome, affords a combined linkage–association approach that merges the advantages of both methods and allows for statistical replication within a single sample (Fulker,

Cherny, Sham, & Hewitt, 1999; Van Steen et al., 2005). By obtaining detailed molecular information about family members, precise estimates of overall relatedness can be obtained, potentially increasing the power to characterize general developmental processes through which genes and environments act and interact with one another (Visscher et al., 2006).

GENERALIZATIONS TO BE MADE ABOUT GENES AND HUMAN BEHAVIOR

Certain patterns have been observed repeatedly enough across diverse behavioral genetic studies that they can almost be considered "laws" of behavioral genetics. Three of these have been enumerated (Turkheimer & Gottesman, 1991; Turkheimer, 2000): first, that all psychological traits are heritable; second, that the effects of being raised in a particular family in general are smaller than the effects of genes; and third, that factors not associated with genes or being raised in a particular family have a large influence on psychological traits. In addition to these, two more axioms can be established: that the direct effect of any one allele on a major psychological trait is relatively small; and that there is substantial heterogeneity in genetic effects on human behavior. There are exceptions to each of these generalizations, but they are relatively few and can be accommodated by minor qualifications.

All psychological traits are heritable. Of the generalizations that can be made about genes and human behavior, the most unequivocal is that all psychological traits are heritable. As explained (Turkheimer & Gottesman, 1991), the null hypothesis of zero genetic influence on any given psychological trait can be rejected a priori and for the most part is no longer empirically contested. Without loss of generality, it can be asserted that all reliably measured traits have some genetic influence, and that to the extent genetic influence is not detected, it is likely due to lack of statistical power, poor psychological (phenotypic) measurement, or both. It is worth noting here that not all behaviors are necessarily heritable (Turkheimer, 1998), but to the extent that individuals reliably differ in their tendency to engage in some sort of behavior, that tendency is almost certainly heritable. For example, whether or not a child notices a particular stimulus presented at a particular moment may be hardly heritable at all; however, their attentional focus on average, across various settings, relative to other children is heritable (Martin, Scourfield, & McGuffin, 2002; Nadder, Silberg, Rutter, Maes, & Eaves, 2001; Sherman, McGue, & Iacono, 1997).

Family-specific environmental effects are relatively small. The effects of family environments are in many ways subtler than those of genes and subtler than would be expected. Overall, the effect of being raised in a particular family is likely to be relatively small – and smaller than either the effects of genes or of environmental factors that differ among family members. This is not to say that family environment does not influence psychological traits. By contrast, it simply states that in the context of genetic research that the family environment itself does not tend to make family members more similar to one another. Similarities among

family members are generally more attributable to the fact that they share genes in common than to the fact that they share the same environment. Again, for behavioral geneticists, environmental factors instead tend to make family members different.

There are many important exceptions to the general trend that the effects of being raised in a particular family are relatively small. Certain psychological traits, for example, appear to be more influenced by the family-specific factors than others. Traits related to altruism and prosocial behavior, for example, may be influenced by family-specific environmental effects more than other traits (Bergeman et al., 1993; Krueger, Hicks, & McGue, 2001). Similarities between relatives in these traits may be attributable to the effect of being raised in the same family more so than is generally the case.

Another important qualification is that the relative impact of family-specific environmental effects changes over the course of development. Among children, the effect of being raised in a given family is actually quite large, but by adulthood, the effect of being raised in that family diminishes, and becomes even smaller as one ages. Conversely, the impact of environmental influences specific to each family member increases (Eaves et al., 1997; Koenig, McGue, & Iacono, 2008; Lyons et al., 1995; McCartney, Harris, & Bernieri, 1990). As the original family environment changes, from being a major component of the total environment an individual is exposed to during childhood, to being less of a component in adulthood, its impact decreases. Evidence suggests that current environment influences psychological traits more than past environment (Fraley & Roberts, 2005), and that family of origin environment may be no different in this regard.

Influences not due to genes or family environment are substantial. There are numerous variables, largely unidentified, that create behavioral differences among individuals, even among those who share the same genes and family environment. Identical twins reared in the same family household, for example, tend to be similar to each other in traits such as extraversion, neuroticism, disinhibition, and intelligence (Devlin, Daniels, & Roeder, 1997; McCartney, Harris, & Bernieri, 1990), but are rarely (if ever) truly identical to each other in those domains. Influences impacting one individual but not the other, or impacting them in different ways, tend to cause individuals to become different rather than similar. As noted earlier from a behavioral genetic standpoint, that for many psychological traits the environment tends to act more by creating differences between individuals than by creating similarities among them (Plomin & Daniels, 1987).

Although the exact nature of these factors is largely unknown, certain variables likely contribute to creating observed differences among individuals (Turkheimer & Waldron, 2000). One of the most prominent is measurement error. Many psychological constructs (as phenotypes) are difficult to define or assess, and imprecision in measurement can lead to observed differences between individuals. Even a measurement of intelligence in the same individual will likely differ slightly on different days; if it differs for the same individual on different occasions, then it

is certainly likely to differ between two different individuals on different occasions.

There is some evidence in this regard that more reliable measures tend to have higher heritabilities and tend to be influenced less by nonspecific environmental factors. For example, when reports of personality or psychopathology from multiple sources are aggregated – across self-report, peer report, and observational ratings, for instance – the proportion of variance due to nonshared environmental variance often goes down (e.g., Baker, Jacobson, Raine, Lozano, & Bezdjian, 2007; Wolf, Angleitner, Spinath, Riemann, & Strelau, 2004). Presumably, this is because biases of different reports are being averaged over, decreasing error in the measurement of behavior.

Measurement error is not the only factor that might create differences between individuals, however. Any environmental variable impacting one individual differently than another could contribute to such differences. Accidents, traumas, and random variability among events encountered in daily life are all examples of variables that could contribute to variation among individuals who might otherwise be similar to one another; and it is part of what makes us all uniquely individual.

Effects of common alleles on psychological traits are modest. For major psychological traits, the direct effects of any single allele are likely to be extremely small. It is by now well recognized that human behavior is extraordinarily complex, with many factors involved in a pathway that proceeds from gene expression to the functioning of neurons, to neural systems, and the interaction of these systems with the environment. For any given psychological trait, many genes are likely involved, with variation in any one of these genes likely contributing relatively little to behavioral variation in the general population. If the sizable contributions of environmental factors are considered together with those genes, the effect of a single gene diminishes further.

Comprehensive meta-analyses of multiple behavioral phenotypes provide evidence of this, suggesting that the effects of common alleles are generally modest at best (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). Although there are many initial reports of substantial effects, estimates of effect sizes tend to decrease as more information is obtained in subsequent replications; effects that initially appear considerable generally are shown to be less substantial as further information is obtained (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001). Across numerous psychological domains, replicating effects of alleles has often proven difficult, which may in part be attributable to small effects.

Some evidence does exist to demonstrate where single genes can have dramatic effects on behavior. Fragile X syndrome, for example, can be traced to mutations in the FMR1 gene (O'Donnell & Warren, 2002), Rett syndrome is linked to mutations in the MECP2 gene (Amir et al., 1999), and various other forms of cognitive and psychomotor disabilities have been linked to different nucleotide repeat polymorphisms (Orr & Zoghbi, 2007). However, these polymorphisms and psychological phenotypes are relatively rare; for common polymorphisms and forms of psychological variation, effects are relatively small. In fact, some arguments have been

made that at least some forms of psychopathology, such as psychosis or autism, are influenced by numerous but extremely rare polymorphisms of large effect, each of which may be unique to a particular individual or family (Sebat et al., 2007; Walsh et al., in press). Under this paradigm, common polymorphisms account for relatively little variation in psychopathology, with genetic influences on behavior being idiosyncratic to a particular individual or their relatives.

Heterogeneity of genetic effects on behavior is substantial. One explanation for small overall effects of polymorphisms is heterogeneity of genetic effects among individuals. In the presence of heterogeneity, the effects of any given gene depend on some other variable that differs among individuals – may they be environmental variables, in the case of gene–environment interaction, or other genes, in the case of gene–gene interaction. In the presence of heterogeneity, the overall effect of a gene in the population might be relatively small, even though it has considerable effect among individuals, because the effects differ from individual to individual.

As a simplified example, one can imagine a gene strongly increasing a trait in one subgroup of individuals, but strongly decreasing the trait in another subgroup; the overall effect in the population might be quite insignificant, assuming approximately equal proportions of individuals in each subgroup. Substantial evidence now indicates that heterogeneity of genetic effects on behavior is important. Although the causes of this heterogeneity might not be fully understood for many psychological traits, it nevertheless appears clear that heterogeneity of genetic effects per se is common.

Returning to family and twin designs, these have demonstrated that genetic effects vary depending on environment or vice versa. In many cases, genes interact with the environment in their effects, with the magnitude or nature of a genetic effect depending on environmental background. In these cases, it is somewhat misleading to focus on overall genetic effects, because the genetic effects depend on environmental circumstances. Intelligence, for example, is significantly less heritable in disadvantaged environments and more heritable in more advantaged environments (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). Similar patterns are observed with misconduct and antisocial behavior, which also appears less heritable in disadvantaged family environments and more heritable in more advantaged environments (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007; Tuvblad, Grann, & Lichtenstein, 2006). Association studies, likewise, have documented that the effects of environmental factors may depend on individual polymorphisms. The effect of maltreatment on antisocial behavior may depend on monoamine oxidase A (MAOA) polymorphisms; for example, maltreatment appears to increase antisocial behavior and misconduct more among individuals who have polymorphisms conferring low MAOA activity (Caspi et al., 2002; Kim-Cohen et al., 2006).

The effects of genes may also depend on other genes, leading to *epistatic* effects on psychological phenotypes. In these cases, genes interact with other genes in their effects, due to a variety of possible reasons,

such as regulatory effects of one gene on the expression of another gene or physical interactions between products of gene translation. The catechol-*O*-methyltransferase (COMT) gene is involved in the breakdown of catecholamine neurotransmitters, such as dopamine, and has been shown to interact with various other genes to influence neurocognitive functioning, particularly prefrontal processes involved in attention and working memory. Evidence suggests that COMT influences expression of a G-protein regulatory protein gene (RGS4) in the frontal cortex (Lipska et al., 2006) and that these two genes interact to influence psychosis (Nicodemus et al., 2007) and related neurocognitive processes (Buckholtz et al., 2007). COMT has also been shown to interact with a metabotropic glutamate receptor gene (GRM3) to influence neural activation during working memory tasks (Tan et al., 2007). Possible evidence of genomewide gene–gene interaction is also evident in family designs, although these effects tend to be comparatively small (Hill, Goddard, & Visscher, 2008) and have other possible explanations, such as genetic dominance, in which polymorphisms at the same locus differ in the magnitude of their effect (Keller, Coventry, Heath, & Martin, 2005).

DELINEATING PSYCHOLOGICAL CONSTRUCTS: THE INTERDEPENDENCE OF PSYCHOLOGICAL AND GENETIC INQUIRY

One of the key developments in behavioral genetics is growth of its influence beyond inquiry into what causes differences in psychological traits, to additionally delineate what the traits fundamentally are. Although distinctions between causes and definitions can be difficult to make, behavioral genetic designs are increasingly being used to define behaviors, in addition to explaining why those behaviors occur. Questions about what constitutes the core features of traits, and at what level of analysis to define constructs, have risen to prominence as genetic designs have increased in sophistication and genetic inquiry has become more detailed in focus. This renewed commitment to defining psychological constructs, in turn, has helped improve the quality of behavioral genetic analysis.

Traits as etiologically coherent composites of behavior. Behavior genetic designs have special utility in defining psychological traits because they help provide an etiologic anchor point in measurement. Many psychological constructs are somewhat abstract, comprising composites of individual behaviors that differ slightly despite the fact that they reflect some common trait. Components of extroversion, for example, include subtraits such as positive emotionality, sociability, and dominance (Lucas, Diener, Grob, Suh, & Shao, 2000; Watson & Clark, 1997). Because of this abstractness, it can sometimes be difficult to know what comprises the core features of a trait – the features that cohere together and distinguish the trait from other traits – and what comprises secondary features – those that may not cohere as strongly or might reflect other traits as well. Behavioral genetic designs help resolve this dilemma by identifying

features of traits that tend to be coinherited – that is, those that tend to correlate particularly strongly across relatives.

Figure 1 can be used to illustrate the logic of how family, twin, and adoption designs might be used to refine the measurement of psychological traits. As noted, the correlation between a psychological feature P_1 in one relative and feature P_2 in another relative is modeled in terms of correlations between relatives' genetic and environmental backgrounds (*g* and *c*, respectively). However, there is no reason why P_1 and P_2 need to be the same feature in different relatives: P_1 and P_2 could be different features in the relatives, such as positive emotion in one relative and sociability in the other, or verbal reasoning in one and working memory in the other. By determining which groups of features most strongly cohere in families according to patterns of genetic relatedness, one can begin to determine which features share common genetic influence and cohere as indicators of a single construct. Observing that positive emotionality and sociability tend to be strongly and predictably correlated across relatives suggest that those features represent the core of extroversion, for example.

Following through on this logic, behavior genetics has helped clarify the outlines of psychological traits, to delineate the structure of those traits, and what their core features are. Studies of common forms of psychopathology, for example, have indicated that problems such as anxiety, depressions, phobia, and panic all share the same genetic and environmental liability, tending to be coinherited at relatively high rates compared to other combinations of psychopathology. Such patterns of coinheritence suggest that these types of problems reflect an underlying trait, generally referred to as "internalizing" (Achenbach, 1966; Kendler, Davis, & Kessler, 1997; Kendler, Prescott, Myers, & Neale, 2003; Krueger & Markon, 2006). Similarly, studies indicate that problems related to substance use, aggression, misconduct, and antisocial behavior problems share the same genetic and environmental liability, tending to be coinherited at relatively high rates compared to other combinations of psychopathology. These patterns of coinheritance suggest that these problems reflect an underling trait, generally referred to as "externalizing" (Achenbach, 1966; Kendle et al., 1997; Kendler, Prescott, Myers, & Neale, 2003; Krueger & Markon, 2006), related to but distinct from internalizing psychopathology.

Delineating the ways that these forms of psychopathology are coinherited helps establish an etiological basis for distinctions between traits, defining etiological boundaries between constructs. Problems such as anxiety and depression have been known to phenotypically covary with one another in ways that are consistent with them reflecting a unitary trait. Finding that they are coinherited among relatives in similar patterns helps strengthen this argument by providing an etiological basis for their shared variance. Equally important is what is not coinherited – internalizing forms of psychopathology, for example, are more strongly coinherited with each other than with externalizing forms of psychopathology. Depression in one sibling, for example, is more strongly predictive of anxiety in another sibling than it is of aggression. Determining which psychological features tend to covary across relatives, and which features tend to covary less so, helps clarify the nature of psychological traits.

Consistent with this, studies have generally found that patterns of genetic and environmental relationships tend to parallel phenotypic relationships. Psychological features that are phenotypically correlated tend to be influenced by similar genetic and environmental factors, and features that are phenotypically uncorrelated tend to be influenced by different liabilities. In the realm of personality and psychopathology, patterns of phenotypic, genetic, and environmental relationships between different measures are all very similar (see Markon, Krueger, Bouchard, & Gottesman, 2002, for discussion). Personality traits related to negative emotionality, for example, are phenotypically, genetically, and environmentally related to measures of internalizing psychopathology, such as depression. This general pattern provides etiologic support for the practice of defining psychological traits on the basis of phenotypic characteristics and also provides support for using genetic studies to aid in their definition.

Endophenotypes. One explanation for parallels between phenotypic, genetic, and environmental relationships is that genetic and environmental influences must be mediated through the same neuropsychological systems that ultimately govern behavior. These neuropsychological systems act as substrates for behavior, providing the structure on which genes and environment impinge, and from which behavior emerges. To the extent that these neuropsychological systems have a particular organization, then that organization will be paralleled in the relationships between behaviors as well as in the relationships between genetic and environmental influences on those behaviors.

As behavioral genetic inquiry has become increasingly molecular in focus, the question of which psychological phenotypes should be examined has been increasingly scrutinized. In particular, it has been argued that attention should focus on phenotypes that are more directly related to the neuropsychological substrates underlying behavior rather than on the behaviors themselves. These endophenotypes, as they are called, should be causally "closer" to the genetic and environmental influences on behavior and more directly reflect the neuropsychological systems mediating those influences (Gottesman & Shields, 1972, 1973). Genetic effects on these endophenotypes should theoretically be larger than the effects on the behaviors themselves, because they occupy a more intermediate position in the causal chain from a specific gene to a specific behavior.

Figure 2 illustrates the rationale behind the use of endophenotypes in behavioral genetic inquiry. In the figure, the effects of genetic and environmental variables on observed behavior proceeds through a chain. This chain begins with the genetic and environmental variables themselves, which influence an endophenotype, which in turn influences a psychological trait, which influences various specific behaviors. According to this chain-like model, the behavioral effects of particular genes or environmental variables are relatively small in part because the effects must propagate through a chain of influence, with behavior being relatively distal from the original genetic and environmental influences. By targeting an endophenotype – a phenotype that is more proximal to the original genetic and

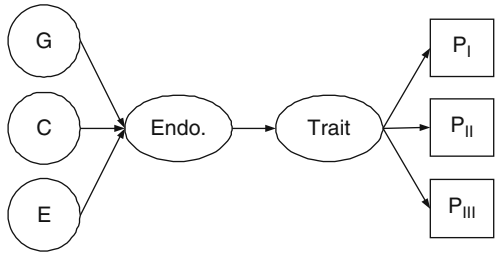

Figure 2. Simplified endophenotype model. *G*, *C*, and *E* represent genetic, family environmental, and nonshared environmental factors, respectively. *Endo.* represents an endophenotype influencing a trait, which in turn influences three observed behavioral phenotypes *P*. *Subscripts* indicate the three phenotypes, measured within individuals.

environmental influences – effects are not propagated as far and should be larger.

Figure 2 is a simplified representation, especially in that there are multiple endophenotypes in any given causal chain, with numerous intermediates linking individual genetic and environmental influences to behavior. In this regard, any number of endophenotypes could be used to study genetic and environmental effects. An endophenotype could be a measure of gene expression, a marker of an expressed protein, an indicator of cellular or neural activity, performance on tasks designed to assess fundamental neuropsychological processes, or even an assessment of traits assumed to underlie behavioral criteria (e.g., traits as indicated in Figure 2). What is considered an endophenotype will vary from study to study depending on its focus and purpose. In the context of studying mental disorder, for example, underlying personality traits or cognitive abilities could serve as endophenotypes. In the context of studying those traits or abilities, other phenotypes, such as neurobiological markers, might be used. Ultimately, using a variety of endophenotypes, across a variety of levels of analysis, is likely to be most useful (Cannon & Keller, 2006).

Various criteria for defining endophenotypes have been proposed (Cannon & Keller, 2006; Gottesman & Gould, 2003). Heritability is invariably considered a criterion, but it is unlikely to be of use in practice as nearly all reliably measured psychological features are heritable to some extent. It is also frequently suggested that an endophenotype possess desirable psychometric or statistical properties, such as being measured reliably, or affording maximum inferential power in statistical modeling (Cannon & Keller, 2006). Such properties are important or necessary in some sense, but may not be sufficient to define an endophenotype, as there are many phenotypes with desirable psychometric and statistical properties that would presumably not function well as an endophenotype. Academic achievement or religiosity are such examples, both being heritable (Koenig, McGue, & Iacono, 2008; Thompson, Detterman, & Plomin, 1991) and having desirable statistical properties, but difficult to justify as endophenotypes.

A particularly useful criterion, described somewhat differently by different authors, is that an endophenotype functions empirically as a cause

of the traits and behaviors of interest (Cannon & Keller, 2006; Gottesman & Gould, 2003). Depending on what aspects of a causal model one emphasizes, this criterion might be operationalized in different ways. It is frequently suggested, for example, that endophenotypes temporally precede or supersede the outcomes of interest. That is, that endophenotypes prospectively predict outcomes, or are more temporally stable. It is also frequently suggested that endophenotypes be genetically related to the outcome of interest, as indicated by family, twin, or adoption studies. These criteria all essentially define an endophenotype as causally impacting the outcomes of interest. In this sense, an endophenotype can be defined as a variable that is causally related to an outcome, but is itself influenced by the same genetic or environmental influences as the outcome, acting like a statistical mediator of the genetic and environmental effects.

Whether or not endophenotypes are empirically useful in identifying specific genetic and environmental influences on behavior remains to be seen. Flint and Munafo (2007), for example, conducted meta-analyses of associations between COMT, schizophrenia, and multiple schizophrenia endophenotypes. Based on these meta-analyses and a broader review of the empirical literature on endophenotypes, they concluded that there was little evidence that endophenotypes provide greater power to detect genetic effects than other phenotypes. Citing work on model organisms, such as mice and yeast, Flint and Munafo (2007) argue that there is no evidence in the broader literature that behavioral phenotypes demonstrate effect sizes that are significantly different from physiological or other phenotypes (Flint, Valdar, Shifman, & Mott, 2005; Valdar et al., 2006). The authors argue, in fact, that the nature of genetic networks are such that they are inherently complex for most phenotypes, in that the direct effects of any gene are likely to be small because of the large number of factors involved, and because of the complex nature of interactions between these factors.

Nevertheless, it is unclear how well the results of Flint and Munafo (2007) will generalize to other phenotypes and genetic and environmental factors. As they acknowledge, their meta-analysis examined only one polymorphism and one set of related phenotypes and endophenotypes. Moreover, as has already been noted, and as is consistent with their findings, this association demonstrated significant heterogeneity, possibly due to gene–gene interactions (Buckholtz et al., 2007; Nicodemus et al., 2007). Flint and Munafo (2007) note that certain endophenotypes of other constructs, namely neural responses to anxiety and fear (Hariri et al., 2002, 2005), have demonstrated relatively larger effect sizes in genetic association studies. It is possible that as empirical evidence accumulates, and understanding of how to define endophenotypes improves, endophenotypes will demonstrate increased utility.

Hierarchy in psychological traits and genetics. Central to understanding genetic influences on psychological traits is the concept of hierarchy: psychological indicators reflecting an underlying unitary trait generally also reflect meaningful variance not accounted for by the trait. In other words, it is important to understand what is *unique* about a psychological feature as well as what it *shares* with other features. General memory

ability appears to affect diverse memory tests (Carroll, 1993), but those memory tests also reflect meaningful variance not shared with the general factor; some tests also reflect visual memory, verbal memory, and other types of memory. To treat a visual memory test solely as a measure of general memory, or solely as a measure of visual functioning, could neglect important insights into the etiology of either form of memory.

Hierarchy is critical to understanding genetic effects on a behavior because what affects a set of psychological indicators simultaneously – that is, what affects a common underlying trait – may be different from what affects each indicator individually. Two examples of this are illustrated in Figure 3. In the first case – known as the "independent pathways model" – each indicator (P) is directly influenced by shared genetic (G) and environmental influences (C, E), as well as genetic and environmental influences unique to each indicator (e.g., G_{II}, C_{II}, E_{II} uniquely influencing P_{II}). In the second case – known as the "common pathway model" – each indicator is influenced by genetic and environmental influences on an underlying trait, as well as genetic and environmental influences unique to each indicator. In both cases, each indicator is impacted by influences that are shared with other indicators, as well as influences that are specific to that indicator. In the common pathway model, the shared influences are mediated through an underlying phenotypic trait; in the independent pathways model, these shared influences affect the indicators directly.

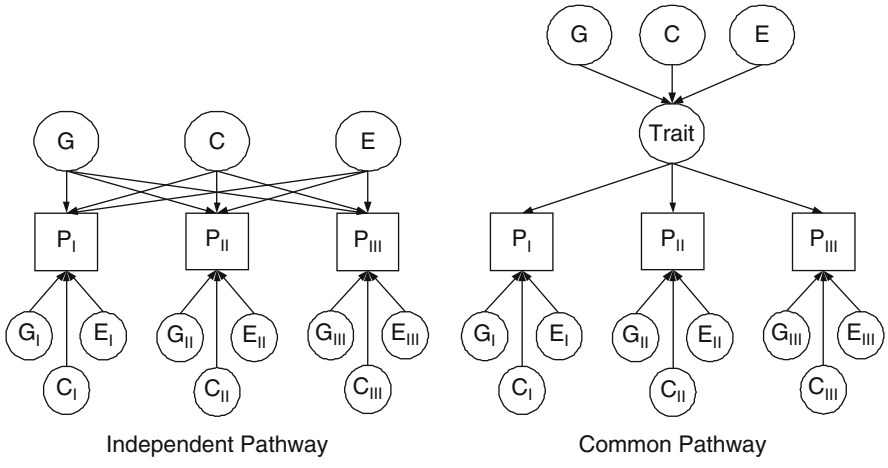

Figure 3. Independent and common pathway models. *G*, *C*, and *E* represent genetic, family environmental, and nonshared environmental factors affecting all three phenotypes *P* jointly. *G*, *C*, and *E* appearing with *subscripts* (*I*, *II*, and *III*) represent unique genetic, family environmental, and nonshared environmental factors affecting a single phenotype.

Substance use and abuse provide compelling examples of how important hierarchy is to behavioral genetics. Use of a given substance is likely to be influenced by factors unique to that substance, such as factors related to metabolism or receptor availability of the substance. It is also influenced by factors shared with other substances, such as

factors related to appetitive reward systems and those shared with other behaviors like disinhibition. Alcohol use is influenced by the alcohol dehydrogenase gene, which affects metabolism and degredation of alcohol (Luczak, Glatt, & Wall, 2006). It also appears to be influenced by genetic factors influencing other substances as well, such as the mu-opioid receptor gene (Barr et al., 2007; Schinka et al., 2002), and by genetic factors influencing general externalizing behavior, such as the muscarinic acetylcholine receptor M2 gene (CHRM2) (Dick et al., 2008).

With reference to substances more generally, there is evidence from twin designs that genetic factors specific to a given substance tend to primarily affect initiation and use, and that substance abuse problems tend to be influenced primarily by genetic influences shared among multiple substances. Examining use and abuse with cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates, Kendler and colleagues (Kendler, Jacobson, Prescott, & Neale, 2003) demonstrated that use was influenced by a general genetic factor (G in Figure 3), as well as substance-specific genetic and environmental factors (e.g., G_I, G_{II}, G_{III} in Figure 3). Substance abuse, in contrast, appeared to be primarily influenced by the general genetic factor as well as environmental factors, without substance-specific genetic factors. Family environment appeared to act through a general factor (C in Figure 3) for both use and abuse. These observations are important in that they suggest that the etiologies of substance use and abuse are different. One might conclude, for example, that attempts to identify specific genes associated with substance abuse are most likely to be successful if multiple substance abuse issues are examined simultaneously.

A hierarchical approach to analyzing genetic effects on psychological traits can be quite useful in determining whether particular indicators reflect particular etiologic influences more than other indicators. An independent pathways model, for example, might suggest that the indicators are relatively direct markers of a shared etiologic influence; a common pathway model, in contrast, might suggest that the etiologic influence is more directly related to an underlying trait rather than the indicators themselves. Similarly, if one indicator was influenced by the underlying shared etiology more than other indicators that indicator might be weighted more in identifying genes affecting all the indicators simultaneously. By identifying which phenotypic features appear to be more strongly related to underlying etiologic variables, one might be able to define endophenotypes more successfully.

An emerging literature has helped identify how traits are hierarchically influenced by genetic and environmental factors. Studies in twins, for example, suggest that major personality traits may differ in how their genetic and environmental influences are mediated. Extroversion and neuroticism may largely mediate the genetic and environmental influences on specific subcharacteristics related to these traits (e.g., positive emotion, sociability, dominance, emotional lability, anxiety) (Johnson & Krueger, 2004). Traits such as agreeableness, conscientiousness, and openness, in contrast, may be influenced by genetic and environmental factors that act directly on their specific subcharacteristics (Johnson &

Krueger, 2004; Jang, Livesley, Angleitner, Riemann, & Vernon, 2002). Different forms of psychopathology may also be differentially related to underlying genetic and environmental influences. Schizotypal personality disorder and schizoaffective disorder, for example, may more directly reflect the shared etiology of psychotic disorders than other forms of psychosis (Cardno, Rijsdijk, Sham, & McGuffin, 2002; Kendler et al., 2006). Similarly, avoidant personality disorder seems to more directly reflect the shared genetic etiology of anxious–fearful personality disorders, whereas dependent personality disorder seems to more directly reflect their shared environmental etiology (Reichborn-Kjennerud et al., 2006).

EMERGING ISSUES AND THE FUTURE OF PSYCHOLOGY AND GENETICS

As inquiry into genetic influences on human behavior has progressed, questions have shifted from broad issues of whether genes or environment influence behavior, and how much, to issues of exactly how genes and environment influence behavior. Currently, the greatest opportunities for progress are arguably in understanding the precise mechanisms by which genes and environmental factors exert influence and how they interact during development to impact psychological processes. This chapter has outlined some of the challenges to understanding these mechanisms, as well as opportunities for improving it.

It is difficult to predict what issues will become most prominent as research into the psychological genetics continues. However, some emerging issues are likely to receive increasing attention as research progresses. Already, critical questions have arisen about how to statistically model the large quantities of genetic information that are being obtained on individuals. The amount of genetic data obtained on individuals is quickly outstripping current methods for drawing conclusions from it, and how to approach the modeling of this data will likely receive increased attention. Also, perhaps more importantly, current understanding of how fundamental genetic processes operate is profoundly changing in some areas. It is increasingly being recognized, for example, that the ways genes are expressed (epigenetic factors) are just as important as the identity of the genes themselves (e.g., Fraga et al., 2005; Mill et al., 2008). New forms of genetic variation are also being identified and are revising our understanding of how individuals differ genetically from one another (e.g., copy number polymorphisms). These new insights into fundamental genetic processes have important implications for studying human behavior. Recent research indicates that identical twins are not in fact genetically identical; although identical twins may share the same versions of genes, they differ in the number of copies of those genes (Bruder et al., 2008) and how those genes are expressed (Fraga et al., 2005). Incorporating new insights about genetic processes into our understanding of psychological processes, and vice versa, will undoubtedly yield important insights into human behavior and health in the years to come.

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Part II

Cross-Cutting Issues in Children and Families

3

Understanding Gene, Environment, and Gene × Environment Interaction Effects: The Example of Childhood Externalizing Disorders

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INTRODUCTION

In the past, models of children's social development focused almost exclusively on causal mechanisms believed to be primarily environmental. Oftentimes, parenting styles were implicated as the primary causal factors in the development of children's social and emotional adjustment (e.g., Bates, Bayles, Bennett, Ridge, & Brown, 1991; Hetherington & Martin, 1979; Patterson, 1982). Peer influence on child behavior has also been researched in depth (Berkowitz & Lundy, 1957; Pravder & Israel, 1983), as were adverse environmental conditions such as poverty (Schweinhart & Weikart, 1988). While these causal pathways each have merit, theories of the origins of children's adjustment and maladjustment evolved dramatically during the 1990s to consider increasingly complex transactional systems in which psychological, sociological, and genetic factors are interrelated in their influence on child adjustment (Bates et al., 1991; Bronfenbrenner & Ceci, 1994).

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Over the past 60 years, researchers have used behavior genetics approaches to improve our understanding of the roles of nature and nurture in relation to child development and psychopathology (i.e., Cleveland, Wiebe, van den Oord, & Rowe, 2000; Deater-Deckard, 2000; Ganiban et al., 2007; Ge et al., 1996). The current chapter aims to introduce the rationale and methodology of genetic epidemiology in the context of genetic and environmental influences on childhood externalizing behaviors.

Behavioral genetic studies of humans estimate the relative influences of genes and environment on observable individual differences in human characteristics. By conducting studies with participants who vary in degree of genetic similarity, it becomes possible to estimate the degree of influence that genes and environment exert on a given trait. Although behavioral genetic research cannot determine an individual's genetic risk for specific outcomes, it is a powerful tool that has gained momentum in the field of developmental psychology for examining the etiology of risk and disorder across individuals. It is important to note here that genetic epidemiology and the concept of genetic influences on behavior have often been the cause of controversy among those concerned with development and psychopathology. However, it is crucial to keep in mind when interpreting statistics from behavior genetics research that genetic influences do not imply inevitability or causation, nor do they determine particular outcomes in individuals. Research has found that genes and genetic influences can and do lead to change. Specifically, they change over time, as well as in response to different environmental circumstances. It is likely that most psychological disorders are caused by multiple genetic and environmental factors and that effective intervention efforts can be better designed when both genetic and environmental risk factors are considered (Plomin, 1990).

The ability to disentangle genetic and environmental contributions to psychopathology is important for gaining a better understanding of the etiology, nature, and course of such disorders across development. A major goal of genetic epidemiology is to untangle the complexity of genetic and environmental etiological factors for putative measures of children's mental health. These factors are usually discussed in terms of genetic, shared environmental, and nonshared environmental influences. Genetic factors are those influences that serve to make individuals similar and can be attributed to the genome.

By definition, shared environmental factors include those non-genetic factors and experiences that are shared by family members and that make them similar to each other. Nonshared environmental influences include those non-genetic factors and experiences that are unique to family members and have caused them to differ, in addition to measurement error (see Reiss, Neiderhiser, Hetherington, & Plomin, 2000, for review). Behavioral genetic strategies have been used to examine numerous forms of childhood psychological disorders including depression, anxiety, autism, attention-deficit/hyperactivity disorder (ADHD), childhood bipolar disorder, obsessive compulsive disorder,

and substance use (Derks et al., 2008; O'Connor, Neiderhiser, Reiss, Hetherington, & Plomin, 1998; Rutter et al., 1990; Plomin, Nitz, & Rowe, 1990). Additionally, known "environmental" risk factors for developmental psychopathology such as quality of parenting or peer influence have also been examined for genetic influence (Rubin, Burgess, & Coplan, 2002; Rubin et al., 2004). A full review of this literature is beyond the scope and focus of this chapter; instead, it concentrates on developing an understanding of the logic and methods employed in studies of genetic epidemiology which center on the function of the "genome" and "envirome" (Sham, 1996; Neiderhiser, 2001).

One group of childhood disorders has been chosen to provide examples and illustrations: externalizing behaviors. Such behaviors refer to a wide range of "rule breaking behaviors and conduct problems, including physical and verbal aggression, defiance, lying, stealing, truancy, delinquency, physical cruelty, and criminal acts" (Hann & Borek, 2001, p. 1). Early recognition, as well as knowledge of the mechanisms of stability and change in childhood externalizing problem, is valuable in the design of effective preventions and interventions (Bartels et al., 2007, 2004), due to the fact that childhood externalizing problem behavior has been found to be stable over time. A wide range of childhood externalizing disorders from early childhood until late adolescence, such as attention problems, conduct disorder (CD), and antisocial behaviors (ASB), have been examined using behavioral genetic strategies (e.g., Bartels, 2007; Burt, Krueger, McGue, & Iacono, 2001). Both childhood and adolescent ASB can pose grave societal problems given that individuals under the age of 18 commit approximately one-fifth of overall crimes in the United States (Tackett, Krueger, Iacono, & McGue, 2005). Childhood ASB in particular has demonstrated considerable continuity and is one of the strongest predictors of later crime, alcohol, and drug abuse (Cadoret, Troughton, Bagford, & Woodworth, 1990; O'Connor, McGuire, Reiss, Hetherington, & Plomin, 1998), as well as ASB in adulthood (Eley, Lichtenstein, & Moffitt, 2003). Research has consistently found that the higher the number of ASB in childhood, the greater the probability that an adult antisocial personality diagnosis will be given (Cadoret et al., 1990). Moreover, it has also been found that these disordered behaviors co-occur at greater-than-chance levels, a finding that has raised important questions regarding the distinctive nature of childhood externalizing disorders.

In this chapter, an introduction will be provided to the research designs and methodological concepts commonly utilized in quantitative genetic studies (Table 1). Family, twin, adoption, and combination study designs will be discussed and examples of each will be presented. Furthermore, aspects of the interplay between genes and environment, including genotype–environment correlations and interactions, will be explored and the current and future directions for the study of genotype–environment interplay will be discussed. These issues will be examined through a review of the behavioral genetic literature on ADHD, ASB, and CD.

Table 1. Research Designs Utilized in Quantitative Genetic Studies

Type of Design	Sample	Purpose of Design
Family studies	An individual with a trait or disorder and relatives	Determines the "familiality" of a trait or disorder of interest
Twin studies	Monozygotic and dizygotic twins	Estimates the degree of influence that genes and environment exert on a given trait
Adoption studies	Adoptees and adopted parents and/or birth parents	Estimates the degree of influence that genes and environment exert on a given trait. Particularly useful for estimating shared environmental influences
Combination designs	MZ and DZ twins and their siblings; MZ and DZ twins reared apart; adoptees and siblings and/or non-adoptive control siblings	Maximizes the potential generalizability and power of studies

FAMILY STUDIES

In a family study, a disorder of interest (e.g., conduct disorder) is examined to assess whether it is more common in the relatives of an individual affected by the disorder than in the relatives of an individual who is not affected by the disorder and who match on many important characteristics (Waldman, 2007; Kendler, 1997). Family studies are a fairly straightforward approach to understanding how mental health is transmitted through families (see Zhao et al., 1997, for review). Parents, siblings, and offspring (first-degree relatives) are most useful in family designs, although the inclusion of more distantly related individuals can aid in distinguishing genetic from environmental influences (Sham, 1996). One shortcoming of the typical family design used in psychiatric epidemiology is that it remains difficult to discriminate between genetic and shared environmental influences. Specifically, if an individual shares both genes and environment with the other family members assessed, the two influences cannot be distinguished from one another. Therefore, despite the simplicity and ease of collecting family histories and conducting assessments for such studies, this method's usefulness (on its own) in discerning genetic and environmental influences is limited (Merikangas & Swendsen, 1997).

Family studies have focused on both internalizing disorders such as childhood depression (Klein, Lewinsohn, Seeley, & Rohde, 2001; Wickramarantne, Warner, & Weissman, 2000) and externalizing disorders such as juvenile obsessive compulsive disorder (Reddy et al., 2001) and have provided valuable information to researchers regarding childhood psychiatric disorders. Although less commonly used today, family studies are an important starting point in behavioral genetics research. Such studies allow for the identification of specific patterns of transmission, thus indicating the familiality of a disorder in question (Merikangas &

Swendsen, 1997). However, to distinguish between genetic and shared environmental effects, twin and adoption studies are needed.

TWIN STUDIES

By contrasting the similarities of monozygotic twins (MZ) and dizygotic (DZ) twins who share their rearing environment but differ in their genetic similarity, genetic and environmental influences may be estimated for measured behaviors, including childhood externalizing disorders (Waldman, 2007). Twin studies take advantage of the fact that MZ share 100% of their segregating genes while DZ twins and full siblings share 50% of their segregating genes, on average. Whereas MZ twins result from the splitting of a single fertilized egg into two genetically identical individuals, DZ twins are the result of two separate eggs fertilized by two different sperm. DZ twins, therefore, are as genetically similar as any other nontwin full sibling pair. This natural experimental design allows genetic and environmental influences to be estimated based on the similarity of MZ and DZ twins – how much a child resembles her co-twin. For example, if only genetic influences on a particular measured construct are important, MZ twin pairs will be twice as similar as DZ twin pairs.

Genetically informed research designs involving twins estimate the relative contributions of genetic, shared environmental, and nonshared environmental influences. Recall that shared environmental influences are those non-genetic influences shared by family members that make them similar and that nonshared environmental influences are non-genetic influences that make family members differ from one another. In twin studies, correlations for both MZ and DZ twins that are significant and do not vary by zygosity indicate that shared environmental factors are operating to make siblings similar. Nonshared environmental influences are indicated when the correlation for MZ twins is less than 1. A critical assumption of twin studies is that both MZ and DZ twin pairs are exposed to similar environmental characteristics that influence a disorder or trait (Waldman, 2007). Ultimately, if MZ twin pairs who were reared in the same home display phenotypic dissimilarity, nonshared environmental factors are indicated. Twin studies are particularly helpful in understanding both genetic and environmental contributions to variations within a particular disorder and covariation among co-occurring disorders (Burt et al., 2001; Burt, McGue, Krueger, & Iacono, 2005).

Many new techniques have been developed to disentangle genetic and environmental influences in the study of childhood externalizing disorders (Burt, Krueger, McGue, & Iacono, 2003; Eaves et al., 1997; Klump, Burt, McGue, & Iacono, 2007; Nadder, Silberg, Eaves, Maes, & Meyer, 1998). Longitudinal behavioral genetic studies allow for the investigation of the extent to which genetic and environmental influences contribute to stability and change across the life span. Longitudinal designs are advantageous because they improve power by making use of observations from the same

individual over time as well as allowing for the examination and estimation of time-dependent genetic and environmental effects. By combining techniques from structural equation modeling and time series analyses and applying them to childhood genetic epidemiology, it is possible to disentangle the independent effects of genetics and environment over time (Bartels et al., 2007). Generally, stability in most of the studied measured behaviors has been due to primarily genetic and shared environmental factors while nonshared environmental influences typically influence change and/or are age-specific.

One study that used a longitudinal behavioral genetic design to examine childhood problem behavior is the Young Netherlands Twin Register (Y-NTR; Boomsma et al., 2006). The Y-NTR includes data on twins from birth to age 12 and uses a multiple informant design including reports from mother, father, child, and teacher. The inclusion of data from more than one informant is important because children's behavior tends to vary across settings. Thus, the behavior that a parent may see and report on is likely to be different than that reported by teachers and child self-reports should include behavior across multiple settings. Data from multiple settings and multiple raters, therefore, provide the most valid measurement of behavior (Scourfield, Van den Bree, Martin, & McGuffin, 2004). Findings from the Y-NTR on the development of problem behaviors from ages 3 to 12 showed that, for all behavioral phenotypes examined, additive genetic influences explained the bulk of the individual differences. Moreover, genetic influences on constructs like aggression showed a great deal of change throughout development with the proportion of genetic influences both increasing and decreasing and new genetic influences contributing to the variance over time. On the other hand, the genetic influences on attention problems were relatively stable across development with little evidence of new genetic influences contributing through the developmental period studied (Bartels et al., 2007). The broad construct of externalizing behavior stability was explained by additive genetic transmission, which accounted for much of the stability over time for boys and for girls (Bartels et al., 2004).

Genetic and environmental processes in the stability and change of aggression from early childhood to adolescence were examined in the Y-NTR sample by testing whether the sources of genetic variation were similar between the ages of 3 and 12 (Bartels et al., 2003; van Beijsterveldt, Bartels, Hudziak, & Boomsma, 2003). Using a simplex model (Loehlin, 1996), aggression was found to be a highly stable behavior from ages 3 to 12 and was largely accounted for by genetic factors (van Beijsterveldt et al., 2003). The results indicated an underlying mechanism of genetic effects and suggested "a dynamic developmental process consisting of transmission of existing genetic effects interacting with new genetic influences" (van Beijsterveldt et al., 2003, p. 601). Moreover, at age 7, a period in which children undergo many developmental transitions, the influence of new genetic factors was found to be large (van Beijsterveldt et al., 2003).

It has been well established that aggression, a core feature of both CD and ASB, endures into adulthood (van Beijsterveldt et al., 2003) and

runs in families (Miles & Carey, 1997). Twin studies examining genetic and environmental influences on childhood aggression have, however, yielded somewhat inconsistent findings (Miles & Carey, 1997). Some studies report large genetic effects (Gottesman, 1963; Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007) while others find little evidence of genetic influence on aggressive behavior (Reznikoff & Honeyman, 1967; Owen & Sines, 1970). A meta-analysis of studies examining genetic and environmental influences on aggressive behavior found an overall genetic effect that accounted for up to 50% of the variance in aggression (Miles & Carey, 1997). Additionally, both genetic and common environmental factors influenced aggression among individuals younger than 18. However, from age 18 and older the influence of common environmental factors was found to be insignificant and only genetic influences were found to be significant, indicating that the heritability of aggression varies with age (Miles & Carey, 1997).

More recently, other genetically informed studies have examined childhood conduct problems longitudinally (Tackett et al., 2005). The Cardiff Study of All Wales and North England Twins (CaStANET; van den Bree et al., 2007) is a sample derived from a population-based twin registry in which conduct problems of children between the ages of 5 and 17 were examined through the use of parent, teacher, and self-reports. The results of this study were consistent with findings from other longitudinal twin studies with evidence of genetic influences on childhood externalizing problems based on reports from all three informants. When combining parent, teacher, and self-reports on conduct problems, it was found that a common underlying phenotype of pervasive conduct problems could be identified. This underlying phenotype was wholly explained by genetic influences (van den Bree et al., 2007).

It is also possible to examine genetic and environmental influences on the covariation of constructs. This allows for a better understanding of how the components of a behavior operate together and are, or are not, distinct from one another. Dick and colleagues (2005) examined genetic and environmental contributions to comorbitity among ADHD, oppositional defiant disorder (ODD), and CD in a sample of Finnish twins. It was concluded that covariation among these disorders is largely attributed to shared genetic influences, while shared environmental effects were generally nonsignificant. A study of 11-year-old twins from the Minnesota Twin Family Study, which also examined the comorbidity of ADHD, CD, and ODD, found that although genetic factors account for a large portion of variance in each individual disorder, covariation among the disorders could largely be attributed to a single shared environmental factor (Burt et al., 2001). This finding led Burt and colleagues to conclude that a common environmental vulnerability is responsible for the covariation among the three externalizing disorders. A follow-up study conducted by the same group examined whether parent–child conflict is associated with the comorbidity among ADHD, ODD, and CD (Burt et al., 2003). Parent–child conflict accounted for 33% of the covariation among these constructs and most of this covariation was due to genetic factors, although shared environmental factors were still significant. Results concluded that parent–child

conflict seems to serve as a common vulnerability which increases risk for the development of multiple childhood externalizing disorders.

Numerous other twin studies have examined childhood externalizing behaviors such as the Swedish Twin study of Child and Adolescent Development (TCHAD; Lichtenstein et al., 2007), the Finnish Population Register Center (FinnTwin16-25; Viken, Kaprio, & Rose, 2007), and the Wisconsin Twin Panel (WTP; Goldsmith, Lemery-Chalfant, Schmidt, Arneson, & Schmidt, 2007). Twins studies of childhood externalizing psychopathology are largely in agreement that genetic factors are relevant in the development, stability, and change of such disorders. In addition, shared environmental factors impacting the development of externalizing problems are most important during childhood and adolescence while they contribute less in adulthood.

Understanding genetic and environmental sources of variation across the life span provides information regarding distinct developmental patterns which do not emerge in phenotypic analyses alone. The age of children matters for most phenotypes that have been examined; estimates of the influences of genetic factors vary across development. This suggests that genetic and environmental influences play different roles across various developmental periods. It is important to note that differences across studies in the relative weight assigned to genes and environment suggest that while genes and environment play obvious roles in development of pathology, researchers have yet to fully understand their interplay. Furthermore, having multiple informants report on child behavior provides better insight into the behavior in question as well as allows for the magnitude of rater-specific effects to be estimated. Overall, results from twin studies have generally converged on the finding that genetic influences are important to many childhood externalizing behaviors.

ADOPTION STUDIES

An adoption study is another natural experiment or quasi-experimental design that is used in behavioral genetic research. In twin and family studies, it is difficult to distinguish between genetic and shared environmental effects because family members share both genes and environment. One way to remove the confounding influence of shared genes and environment is to compare individuals with the same degree of genetic similarity across different environments. The adoption design is one such powerful method for estimating genetic and environmental effects and understanding the role that environment has on childhood psychiatric disorders (see Haugaard & Hazan, 2003, for review).

There are several different types of adoption studies. In the most common, an adoptee is compared with both his adoptive parents and birth parents on the construct of interest (e.g., Cadoret et al., 1990; Leve et al., 2007). If there is a significant correlation between the adoptee and his adoptive parents, shared environmental influences are suggested since an adoptee shares no genes with his adoptive parents. Genetic influences

are indicated if there is a correlation between the adopted child's behavioral phenotype and his birth parent(s) because the child shares exactly half of his genes with his birth parent(s) but is not being reared by them; thus there are no shared environmental influences. Effects of the family climate on a biological child's outcome may be due to environmental and/or genetic influences in non-adoptive families where the birth parents are rearing their biological child. However, in adoptive families, adoptive parents and the adopted child share only the family environment, not genes; thus any direct influence of the adoptive parents on the child must be due to environmental factors. Adoptive and non-adoptive families can be compared in a way similar to comparing MZ and DZ twins in order to estimate genetic and environmental influences. Specifically, if the correlation between a family factor (such as marital conflict) and child outcome (such as CD) is greater in non-adoptive families than in adoptive families, genetic influences are indicated. If, on the other hand, the correlations are nonzero and approximately the same for the two groups, shared environmental influences are suggested.

Genetic and environmental factors influencing the development of ASB and other problem behaviors have long been a focus of adoption research. For example, (Cadoret et al. 1990) found that adult adoptees with a birth parent with a criminal background who were then placed into lower socioeconomic status (SES) homes had particularly high rates of ASB as adults. An adoption study report by Ge et al. (1996) explored genetic contributions on family environment as evoked by the child. Results indicated that adolescents whose biological parents had two or more disorders displayed significantly greater levels of hostile behaviors as compared to children whose birth parents had no disorders (Ge et al., 1996). This was found to be true as rated by adoptive parents, observers, and clinicians, but not for the child's self-reported antisocial and hostile behavior, and supports the presence of genetic influence on child behavior. It is also worth noting that the effects were larger for children whose birth parents had more than one disorder, suggesting that comorbidity in birth parents increases the genetic risk to the child.

Adoption designs rely on the assumption that adoptees are randomly placed with adoptive families who are no more similar to their birth families in relevant characteristics than would be expected at random. In other words, the children have not been selectively placed in households particularly "like" their birth families. If children are not selectively placed, once intrauterine factors and exposure to environmental toxins have been considered, any similarities between an adoptive child and their birth parents can be assumed to result from genetic factors (Leve et al., 2007). It is possible to ascertain the influence of selective placement if both adoptive and birth parent information is available. Research that has examined characteristics of adoptive and birth parents of individuals adopted at birth has found little evidence for the impact of selective placement (Defries, Plomin, & Fulker, 1994).

The Early Growth and Development Study (EGDS) is a prospective adoption study of adopted children, their birth parents, and adoptive parents (Leve et al., 2007). The primary aims of the study are to disentangle

the effects of genes, prenatal drug exposure, and the postnatal rearing environment. More specifically, various family processes are explored to examine how they mediate or moderate genetic expression of various behavioral and psychological characteristics. Non-genetic longitudinal studies have found that temperamental characteristics in children as young as 3 years of age predict severe ASB and other externalizing behaviors at age 21 (Caspi et al., 1997; Newman, Caspi, Moffitt, & Silva, 1997). Because the EGDS has obtained detailed and longitudinal data on birth parents as well as on adopted children and adoptive families, the study will be able to examine early precursors to problematic developmental trajectories in children at risk for early conduct disorder and antisocial behavior. Ultimately, this will aid in the identification of aspects of the family environment that have potential to serve as targets in prevention and intervention efforts (Leve et al., 2007).

As noted in the section on twin designs, the accurate description and understanding of the etiology of externalizing disorders like ASB, CD, and ADHD is critical especially given the findings that genetic and environmental contributions differ depending on the pattern of symptoms (Hann & Borek, 2001). Adoption studies provide evidence for complex relationships among genetic and environmental factors and help to advance our understanding of the impact of shared environmental factors on childhood externalizing disorders. Adoption designs are also critical for understanding gene–environment correlation, discussed in detail below.

COMBINATION STUDIES

The three approaches typically employed in quantitative genetic research can be combined in various ways into designs that capitalize on the advantages and address the shortcomings of each. A hybrid of twin and adoption designs – the twin/adoption design – is one such combination. Through the use of twin/adoption design the power of a twin design to estimate genetic influences is combined with the power of an adoption design to estimate shared environmental influences. To date, there have been at least three studies that have used such designs: the Swedish Adoption/Twin Study of Aging (SATSA; Charles, Gatz, Pedersen, & Dahlberg, 1999), a subset of the Swedish Twin Registry, the Minnesota Study Twins Reared Apart (MISTRA; DiLalla, Carey, Gottesman, & Bouchard, 1996), and a study of Finnish twins reared apart (Langinvainio, Koskenvuo, Kaprio, & Sistonen, 1984). All of these studies have found that for most personality and cognitive ability constructs examined, genetic influences predominated (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990; Pedersen, Plomin, McClearn, & Friberg, 1988; Tellegen et al., 1988). It is worth noting, however, that in all cases these were research samples recruited and assessed during adulthood when shared environmental influences are known, from longitudinal work, to have less of a direct impact. It is, however, becoming increasingly difficult to obtain a sample of twins adopted apart at birth.

A second type of combination design may include twins and their siblings in the same sample. This type of design helps to maximize the potential generalizability of the findings as any special twin effects can be estimated directly. It is important that spurious differences between the nontwin sibling pairs be minimized in order to ensure that the twin and nontwin groups are as similar as possible. A variation on this design is to include the siblings of twins in the study sample. Both types of combination designs increase the power and generalizability of the studies (Neiderhiser, Reiss, & Hetherington, 2007). Presently, there have been only a few studies that have extended the traditional twin design by including additional sibling types either within the same family or from different families.

One such study is the Nonshared Environment in Adolescent Development project (NEAD; O'Conner, McGuire et al., 1998; Reiss et al., 2000; Neiderhiser et al., 2007). NEAD is a nationwide longitudinal study of twins and siblings in two parent families (including nondivorced and step families) assessed at three separate time points: middle adolescence, late adolescence, and young adulthood (Loehlin, Neiderhiser, & Reiss, 2005; Reiss et al., 1995). In general, findings from NEAD have been consistent with those from twin and adoption designs. One exception to this is that the estimates of genetic influences on ASB have consistently been higher in NEAD than in other reports (e.g., Reiss et al., 2000). Because NEAD used a multi-method, multi-rater approach and created composites across measures and raters, the composite of ASB utilized represents a cross-situational set of behaviors and thus is likely to be more heritable (Saudino & Plomin, 2007).

There has been a wealth of empirical work resulting from NEAD concerning childhood adjustment and externalizing disorders. For example, the genetic and environmental effects on the association between problem solving and ASB were estimated and it was found that while ASB demonstrated genetic influences, problem solving did not (Spotts, Neiderhiser, Hetherington, & Reiss, 2001). Additionally, shared environmental influences were found for both as well as for their association (Spotts et al., 2001). A second finding concerns the co-occurring nature of ASB and depression. (O'Connor et al. 1998) found that genetic influences accounted for the stability of ASB and depression over a 3-year period. Moreover, the co-occurrence of these two disorders was found to be mediated by genetic factors.

Other findings from NEAD concern the covariation between parenting and child adjustment and have found that genetic influences were significant for the cross-lagged association between adolescent adjustment and parenting from middle adolescence to late adolescence (Neiderhiser, Reiss, Hetherington, & Plomin, 1999). Furthermore, the associations between marriage and parenting constructs and child adjustment and maladjustment have also been found to be significantly influenced by genetic and environmental factors (Neiderhiser et al., 2007; Reiss et al., 2000).

There are at least two other studies that have used an extended twin/family design. One of the largest is the National Longitudinal Study of Adolescent Health (Add Health; Beaver et al., 2007a; Harris, Halpern,

Smolen, & Haberstick, 2006). Add Health is similar in design to NEAD with twins and nontwin siblings in a variety of family settings, although Add Health also includes cousin pairs. To date there have been only a few reports from Add Health examining genetic substrates of externalizing behaviors. Beaver and colleagues (2007a) examined the genetic origins to adolescent victimization by aggressive peers and found a genetic predisposition that significantly increased the chances that an adolescent would be the victim of a crime. A second study also found evidence that genetic factors influenced the development of CD and adult ASB in males (Beaver et al., 2007b). A final study has employed an extended twin/family design focused on parenting (Losoya, Callor, Rowe, & Goldsmith, 1997) and found genetic influences on measures of the family environment and a relationship between child-rearing practices and parent personality.

Adoption and sibling studies can also be combined into a sibling/adoption design. Such studies include adopted and non-adoptive sibling pairs enabling another direct test of shared environmental influences. Specifically, if adoptive sibling pairs are correlated at all, shared environmental influences are indicated. The degree to which non-adoptive sibling pairs are correlated more than adoptive sibling pairs estimates genetic influences as non-adoptive siblings share 50% of their segregating genes (on average) and adoptive siblings share none. The Colorado Adoption Project (CAP) is one such study (Rende, Slomkowski, Stocker, Fulker, & Plomin, 1992; Plomin & DeFries, 1985) that examined genetic and environmental influences on various childhood externalizing disorders (Braungart-Rieker, Rende, Plomin, DeFries, & Fulker, 1995; Coon, Carey, Corley, & Fulker, 1992; Rende & Plomin, 1992). Gelhorn and colleagues (2005) examined the heritability of individual symptoms of CD within the CAP. In general, results showed that levels of genetic and environmental contributions to different symptoms of CD varied. Moreover, moderate to substantial levels of genetic influences were found for many items, while the magnitude of shared environmental influences was modest to moderate.

There have been numerous other studies which used extended behavioral genetic design frameworks to estimate genetic and environmental influences on family processes and child maladjustment. The Twin/Offspring Study in Sweden (TOSS; Neiderhiser & Lichtenstein, in press; Reiss et al., 2001) was intended, in part, as a parent-based complement to the child-based NEAD study and is a combination study in that it includes both twins who are parents as well as one child of each member of the twin pair. The Australian National Health and Medical Research Council Twin Registry (ATR; Mendle et al., 2006; Slutske et al., 1997) is a longitudinal study of health and behavior of twin mothers and their offspring in an attempt to delineate the intergenerational transmission of psychopathology and maladjustment associated with divorce. The Virginia 30,000 (Truett et al., 1994) is a study of multiple family members including MZ and DZ twins, and their spouses, parents, siblings, and children. The Netherlands Twin Family Study of Anxious Depression (NETSAD; Boomsma et al., 2000) is a longitudinal behavioral genetic study of adolescent and young adult twins, their parents, and their siblings which examines anxious, depressive, and personality traits.

Taken together, these findings support that combining aspects of the various types of behavior genetic studies, such as adding siblings as they naturally occur in families, is a method that both increases the power of studies and allows for additional conclusions to be drawn from such studies. Additionally, it provides some significant insights into the complex interplay between nature and nurture as well as helps to identify sources of human variation. Interestingly, some of the most important findings from behavioral genetic studies concern sources of environmental influence and therefore have important implications for prevention and intervention programs targeted at treating childhood externalizing disorders.

GENE–ENVIRONMENT CORRELATION AND INTERACTION

Research and theory suggest that genes and environment are intertwined in their shaping of individual development, particularly in families where both genes and aspects of the environment are usually shared by family members. Clinicians and researchers agree that a child's personal characteristics help to shape the environment around them and that parents' personal characteristics and behaviors form a substantial part of the child's environment as well. It is becoming more and more evident that our conceptualization of genetic or environmental causes and risk factors may have excluded the possibility of more complex gene and environment action and coaction. Several possible mechanisms of interplay between genes and environment have been described in terms of gene–environment correlation (rGE) and gene by environment (G×E) interaction, which will be discussed in turn below (Caspi et al., 2002; Rutter, Moffitt, & Caspi, 2006). In the past, these mechanisms were largely ignored for both theoretical reasons and due to computational limitations. However, theory and the definition of rGE and G×E interaction have evolved and expanded to consider these mechanisms as likely rather than assuming them to be rare or absent. Luckily, advances in statistical modeling and the increasing sample sizes in twin, family, and adoption studies have also made it possible to begin disentangling the etiologies of normative and pathological development in terms of gene and environment interplay.

With rGE, heritable characteristics covary with exposure to aspects of the environment. Thus, purportedly "environmental" variables may appear heritable because of this association. The presence of rGE is thought to account for heritability found in measured factors like SES or negative life events (Kendler & Baker, 2007; Lichtenstein, Pedersen, & McClearn, 1992). In general, three forms of rGE have been explored in family research: passive, active, and evocative (Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1988). Passive rGE results from biological family members sharing both genes and environments. This might be best conceptualized using personality characteristics, which have demonstrated significant genetic influences. A parent may exhibit genetically influenced personality traits of negativity and aggression; their child, therefore, may engage in rule breaking and aggressive behavior due to both shared genetic influence on personality and the negative, antisocial environment

created by the parent. When an individual seeks out and actively selects environments that correlate with their genetically influenced characteristics, the result is termed active rGE. Active rGE may be seen when a child who is genetically predisposed to externalizing behaviors seeks out peers who also engage in and reinforce problem behaviors, thereby actively selecting an environment that correlates with his genetically influenced characteristics. The third type of rGE, evocative, is of particular interest to the understanding of family and social processes. Evocative rGE occurs when an individual's genetically influenced characteristics or behaviors elicit reactions from others. In other words, it is the association between a person's genetically influenced behaviors and the reaction of others to this behavior (Jaffee & Price, 2007).

It is easy to imagine this happening within different subsystems of the family: a warm, sociable child may elicit supportive and warm reactions from parents; conversely, a highly irritable child may inadvertently elicit harsher responses and rejection from parents and siblings. Likewise, this reciprocal process has been noted among peers where a child's (possibly genetically influenced) behaviors or personal characteristics elicit support or rejection from other children.

Identifying rGE has been somewhat challenging. For instance, consider a child-based (children vary in genetic relatedness) combination family study that indicates a strong genetic influence on the association between negativity in the parent–child relationship and conduct disorder in the child. Because child-based twin and family designs detect the influence of the child's genes, it might be tempting to interpret these findings as support for the child's heritable characteristics as the main vehicle for genetic influences on both negativity in the parent–child relationship (i.e., some characteristic in the child evokes a negative response from the parent/environment; evocative rGE) and the child's behavior disorder. However, because children also receive 50% of their genes from each parent, a child-based design is unable to decisively disentangle passive from evocative rGE for parenting; the finding may also be due to shared genetic characteristics of the parent and child (Ulbricht & Neiderhiser, 2009). Findings from genetically informed family studies indicate that child-based designs and parent-based designs (parents vary in genetic relatedness) considered together are valuable for beginning to clarify different mechanisms for genetic influence on family relationships (Neiderhiser et al., 2004; 2007; Rutter et al., 2006).

Adoption studies are useful for disentangling types of rGE because they control for passive rGE; adoptive children do not share genes with the parents providing their environment; thus passive rGE cannot explain child behavior. However, additional considerations need to be made with adoption studies, such as the amount of variability in the adoptive families; adoptive parents very often go through rigorous evaluation before being approved for an adoption placement. As a result, when an adoption design includes a sample of biological parents rearing their own children who are matched to the adoptive parents, this approach can be somewhat biased toward finding passive rGE because of the greater variation in the parenting environments found in the larger population of

non-adoptive families than in the more restricted population of adoptive families (Stoolmiller, 1999). However, subsequent reports directly testing Stoolmiller's theory have found that there is adequate variation in adoptive families (McGue et al., 2007).

Another way of estimating rGE is to employ within family comparisons – thus eliminating the confounding factor of between family variation – by comparing biological and adoptive children in the same household (Rutter & Silberg, 2002). Researchers may also use the children-of-twins (CoT) design to disentangle genetic and environmental influences and to specify rGE (Silberg & Eaves, 2004). The rationale for this methodology is discussed briefly below. A more detailed discussion of the logic of the CoT design can be found elsewhere (D'Onofrio et al., 2003). In this design, a twin mother or father, twin aunt or uncle, and target child are evaluated. Using twin mothers as an example, if the twin aunt's parenting is related as strongly to the child's antisocial behavior as the twin mother's parenting, a passive rGE effect is present; however, if the twin mother's parenting is more highly correlated with the child's ASB then direct environmental effects are supported (Moffitt, Caspi, & Rutter, 2005). Several studies have employed the CoT design to examine aspects of child mental health besides ASB (e.g., D'Onofrio et al., 2006; Lynch et al., 2006; Mendle et al., 2006). However, one study in particular addresses the topic areas that are the focus of this chapter.

Harden et al. (2007) utilized the CoT design with a subsample from the Australian Twin Registry to examine the genetic and environmental influences on the association between marital conflict and child conduct problems. Results suggested that, at least in part, marital conflict's association with child conduct problems is due to the child's inheritance factors that influence both marital conflict and conduct problems: passive rGE. However, the authors note that this finding does not rule out the possibility that the genetic factors, rather than being directly associated to parent and child behavior, may instead increase the child's vulnerability to the adverse environment of marital conflict: G×E interaction (Harden et al., 2007). There is also an extended children-of-twins approach (ECoT) which, by adding a sample of twin children and their parents to a sample of twin parents and their children, enables the direct estimation of passive and evocative rGE as well as the direct environmental influences of the parents on the children (Narusyte et al., 2008).

As mentioned previously, evocative rGE is indicated by genetic influences on parenting in a child-based design and will emerge as shared and/or nonshared environmental influences in a parent-based design (Neiderhiser et al., 2004; Ulbricht & Neiderhiser, 2009). Evocative rGE effects on parenting behaviors have been noted in several twin and sibling family designs; the evidence is made stronger by the use of observational and multi-informant measures of parenting to reduce the impact of passive rGE in the form of perceptual bias (Reiss et al., 2000; Rende et al., 1992; Deater-Deckard, Fulker, & Plomin, 1999; Neiderhiser et al., 2004). An extension of the adoption research design to include more birth parent information is also useful in identifying evocative rGE in the development of externalizing behaviors. In such a design, an adoptee's genetic risk

for aggression is established through the biological parent's aggressive behavior or diagnoses; the child's behavior and adoptive parent's parenting are also assessed. Results from three such studies indicate that children who have birth parents who are high on aggressive and antisocial behavior receive more discipline and control (negative parenting) than children who have birth parents who are low on aggressive and antisocial behavior (Ge et al., 1996; O'Connor et al., 1998; Riggins-Caspers, Cadoret, Knutson, & Langehn, 2003). Researchers with EGDS are currently collecting data using a prospective, longitudinal adoption study that includes birth parents and adoptive families (Leve et al., 2007). Even more intriguing, these studies also indicate that it is the child's genetically influenced aggressive behaviors that serve as a mediator or pathway between birth parent factors (genetic risk) and adoptive parenting environment. This effect has also been identified in at least one twin sample of adolescents (Narustye, Andershed, Neiderhiser, & Lichtenstein, 2007). Interestingly, active rGE has not been examined in the same detail as passive and evocative rGE. Recall that active rGE includes processes by which a child's genetically influenced characteristics or behaviors lead them to seek out elements of the environment that match their genotype (Rutter & Silberg, 2002). Active rGE processes are potentially very important to understanding continuity, change, and course of ASB across development. Active rGE can increase a child's likelihood of coming into contact with risky environments; responses to environmental factors may involve G×E interactions. One explanation for the lack of detailed study into active rGE is the difficulty of disentangling active from evocative rGE outside of an experimental design. As the vast majority of research in this area uses quasi-experimental and naturalistic designs, with a focus on questionnaires and behavioral observation, it has not been possible to consider active rGE influences.

G×E interaction has been defined in a number of different ways over the past 20 years, contributing to confusion over exactly what genotype × environment interaction involves. Most broadly, G×E studies focus on how the environment (including the social environment like interpersonal and family relationships) responds to genetic influence and, likewise, how genetic influences may shape the environment (Reiss & Leve, 2007). In G×E, variation in the sensitivity of the environment to genetically influenced behaviors and genetically influenced variations in sensitivity to the environment provide avenues for both risk and resilience over the course of development (Neiderhiser, 2001). G×E interaction may be able to explain some phenomena such as differential reactions to adversity or even differential effectiveness of prevention and intervention techniques (Bakermans-Kranenburg, VanIJzendoorn, Pijlman, Mesman, & Juffer, 2008; O'Connor, 2006). Much of the initial and exciting research focused on G×E interaction concerned a specific gene or set of genes conveying risk or protection in the face of adverse environments. A more thorough discussion of these molecular genetic approaches can be found elsewhere (Lander & Schork, 2006; Neiderhiser, 2001; Plomin, Owen, & McGuffin, 1994); however, initial findings for molecular G×E interaction in the development of child ASB have served

as a basis for more recent quantitative findings and are discussed briefly below.

Caspi et al. (2002) addressed the question "Why does child maltreatment lead to antisocial behavior in some but not others?" The candidate gene chosen was one that codes for an enzyme that breaks down neurotransmitters, monoamine oxidase A (MAOA). Results indicated that individuals with a form of the gene that resulted in high levels of MAOA expression were less likely to develop antisocial behaviors in the presence of child maltreatment than individuals with a different polymorphism of the MAOA gene (Caspi et al., 2002). These differences in antisocial behavior and conduct disorder were most evident in the presence of severe maltreatment; children with different polymorphisms demonstrated generally the same amounts of ASB and CD in the absence of maltreatment (Caspi et al., 2002). This study provides support for the notion that specific genes can influence a child's sensitivity to his or her environment in regard to mental health and behavioral outcomes. However, while links between the MAOA genes and child behavior problems have been replicated (e.g., Foley et al., 2004) there have also been a number of non-replications (e.g., Young et al., 2006). While not discounting the role of genes in general, this pattern of findings supports the likely role of several genes with small effect and/or the presence of subtypes within broader psychopathologies that may reflect the actions of different genes (Reiss & Leve, 2007). Likewise, a limitation to the use of candidate genes in searching for G×E interaction is the small number of known candidate genes as well as the cost of collecting and analyzing DNA samples from participants in studies (though this cost is decreasing).

Furthermore, molecular genetic studies do not generally consider rGE in their analyses, a major limitation when the role of rGE is likely to be important to understanding the interplay of genetic and environmental influences on complex behaviors (Jaffee & Price, 2007; Reiss & Leve, 2007). Recall that rGE "reflects differences in exposure to particular environments" (p. 2) and that the differences in exposure are likely mediated by behaviors rather than the result of direct genetic effect (Jaffee & Price, 2007). By not considering this behavioral step between measured genes and outcome, a crucial piece of the puzzle is missing. This limitation is even more pertinent when considering the roles of genes and environment within family systems where individuals have common elements of both genes and environment (Eaves, Silberg, & Erkanli, 2003). In families, genes common to parent and child may impact "environmental" conditions through the behaviors of either or both individuals. However, there is another approach that uses genetically informative twin and family or adoption studies to estimate what amounts to a genotype by environment interaction. This genotype × E interaction reflects more of an anonymous genetic influence on the environment rather than the impact of a specific candidate gene. For example, Kim-Cohen and colleagues (2004) used a twin design to find that children's resilience in the face of socioeconomic deprivation was influenced both by heritable traits like temperament and by family processes such as maternal warmth and pleasant activities. Button and colleagues (2005) also found that most of the variation in ASB

found in the CaStANET sample was accounted for by the child's genes and their interaction with family disharmony.

In general, researchers and theorists have discussed six types of G×E interaction in the etiology of psychopathology (Neiderhiser, 2001; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Kendler et al., 2005; Tienari, 1991). Type 1 involves increased risk for a certain phenotype only when both genetic and environmental risk factors are present. In this situation, neither genotype nor environment alone is sufficient to cause the disorder. An example in terms of conduct disorder would be if parental rejection (environment) along with a certain genetic profile were highly associated with externalizing behavior but neither the profile nor the parental rejection was linked to problem behavior in the absence of the other. Type 1 G×E interactions are the typical targets of quantitative genetic studies of gene–environment interplay. A recent analysis of the NEAD sample found an interaction between the child's genetically influenced ASB and parental negativity such that the genetic influence on adolescent ASB was greater when there was more parental negativity (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007). Utilizing a relatively recent advancement in analytic strategy (Purcell, 2002), researchers were able to statistically control for rGE, providing a clearer picture of the relationship among a child's genes, behavior, and parenting environment (Feinberg et al., 2007).

In Type 2, environmental influences alone are enough to increase risk, without presence of corresponding genetic risk. This situation would be suggested if all children in one classroom or school exhibited the same disordered behavior, regardless of genetic profile. Alternatively, a Type 3 effect occurs when genetic influence increases phenotypic risk, even in the absence of environmental risk factors. Thus a child with a specific set of genes would be at increased risk of developing conduct disorder, regardless of the quality or variations in the environment. Type 2 and Type 3 effects are not exactly G×E interactions per se, as the term is generally defined; rather, they could be more clearly described as responses to environmental or genetic risk factors, respectively. They are included in this discussion because effects such as these are plausible and should be considered when examining the etiology of psychopathology (Neiderhiser, 2001).

In Type 4 G×E interactions, genes and environment each contribute to risk independently (additively). This would be implicated if children in a certain neighborhood were at increased risk for developing a behavior disorder and children with a certain genotype were at increased risk for developing the behavior disorder but children who were both in the neighborhood and had a certain genetic profile were at the most risk. In Types 5 and 6, a certain genotype becomes either a protective factor (Type 5) or a risk factor (Type 6) for psychopathology, depending on the environment. This idea seems somewhat counterintuitive, but when we consider the broad variation in environments, it makes sense that traits may be adaptive in some situations but cause discord in others.

Over the past 10 years, researchers have placed increasing focus on identifying G×E interactions in the development and course of

externalizing behavior. A number of comprehensive reviews and meta-analyses are available (i.e., Jaffee & Price, 2007; Rutter et al., 2006; Moffitt et al., 2005; Kim-Cohen et al., 2006), though only broad findings and a few individual studies have been discussed here. Identification of rGE and G×E in the etiology of childhood psychiatric disorders has importance in the development of both treatments and preventions (Jaffee & Price, 2007). Much of the trepidation that has historically surrounded behavioral genetic research has understandably stemmed from concern that finding conditions to be genetically based may contribute to victim blaming and deterministic views of psychopathology (i.e., if a disorder is caused by genes, there is no external/environmental intervention to address it). However, the interpretation of behavioral genetic findings of rGE and G×E can have a seemingly contradictory conclusion. Jaffee and Price (2007) point out that, if genes and environment work reciprocally to influence pathology, the outcomes of even highly heritable disorders may be altered by environmental intervention. Essentially, genetically informed studies have the potential to remove the confounding – and difficult to address – genetic factors that can cloud the causal pathway between environmental factors and pathology (Moffitt et al., 2005). Furthermore, Reiss and Leve (2007) propose that findings of G×E interaction in developmental psychopathology suggest a social mediation pathway for genetic effects that provide "environmental" targets for focused interventions that may alter the social environment's response to heritable characteristics, thus reducing the effects of genetic risk.

CONCLUSIONS AND FUTURE DIRECTIONS

Quantitative genetic studies provide information that is central to the development of models of developmental processes. This information can be used to expand our understanding of how children with a certain set of characteristics and genes develop both adaptive and maladaptive behaviors as a function of environmental influences. Such studies have also allowed researchers to test the direction of the associations between parenting and child adjustment (Narusyte et al., 2008), thus furthering our understanding of how parenting and family processes interact with unique child characteristics to impact the development of problem behaviors. Findings from behavioral genetics research can be used to inform preventive interventions designed to improve the mental health and well-being of children (Leve et al., 2008).

Twin, adoption, and combination designs are used to estimate the effects of an individual's entire genotype. However, such studies do not reveal which genes are involved in the expression of behavior nor the specific polymorphisms that are involved. Increasingly, researchers are employing molecular genetic designs in which genes associated with particular psychiatric disorders are located and identified. Both allelic association and linkage studies utilize DNA markers involving variations in DNA. Currently, there are thousands of DNA markers available. This

allows researchers to locate genes that are causally connected with a disorder without knowledge of the specific mechanism involved in the gene's mode of expression.

Rapid advances in molecular genetics along with methodological advances in behavioral genetic studies are allowing researchers to examine the interplay between genes and environment in ways that were not previously possible (Neiderhiser & Lichtenstein, 2008). While the fields of behavioral and molecular genetics are currently somewhat independent, both approaches are increasingly being employed within single research studies, thus providing the opportunity to examine the associations between specific polymorphisms and specific genetically influenced behaviors throughout development. For example, a specific polymorphism associated with phenotypic behaviors characteristic of ADHD can be identified, screened for, and considered in the treatment design. Different approaches to analyzing and presenting effects of joint and independent genetic and environmental risk factors have been suggested, including an epidemiological approach that focuses on effect estimation rather than model fitting (Botto & Khoury, 2001). Such analyses use discrete variables (such as presence or absence of the risk factor) to provide separate odds ratio assessments of the effects of individual and joint risk conferred by a certain genotype or exposure to environmental risk (Weiss, 2007).

This discussion also highlights the fact that the term "environment" in rGE and G×E interaction in families has an increasingly complex meaning beyond that of the traditional psychosocial concept of environment. There is increasing evidence that one's environment can moderate the expression of genetic influences on psychopathology (Reiss & Leve, 2007). As this issue is explored further, researchers must look at extreme conditions in addition to "normative" samples as there may be different mechanisms at play. The ability to identify and specify types of rGE, which currently few studies are able to do, is an exciting new direction for behavioral genetic research (Neiderhiser & Lichtenstein, 2008).

It is important to consider the implications that findings from behavioral genetic studies have for preventive interventions for children with externalizing disorders such as ASB, ADHD, and CD. It is often thought that results are based on differences between groups of people. However, heritability is a statistic that describes the contribution of genetic differences to observed differences among individuals in a particular population at a particular time (Plomin, 1990). Findings can be used to create interventions, but these interventions must take into account the plethora of influences that account for human behavior.

EGDS, for example, is a study which combines knowledge gained from an adoption study design with knowledge gained from preventive intervention trials to "inform the development of highly specified, genetically informed preventive intervention trials" (Reiss & Leve, 2007, p. 1020). By using this prospective and longitudinal approach that includes and follows birth parents, adopted children, and adoptive families, the interplay between genes and environment through both rGE and G×E can be examined with the intention of focusing on developmental mechanisms.

The field as a whole is moving toward merging knowledge across various disciplines such that focused interventions will consider specific genetic influences as well as environmentally mediated and environmentally moderated effects on behavior. Such translational work will allow results from quantitative and molecular genetic designs to be directly applied to preventions and interventions designed to benefit children and families (Reiss & Leve, 2007). Behavioral genetic studies that consider the ways in which the combined effects of neurobiological processes, genetic factors, and unique to the family environments together may result in maladaptive trajectories of childhood externalizing disorders are becoming increasingly popular.

Theory-based developmental models specifying genetic and environmental influences on child psychopathology could someday be applied to psychosocial interventions to modify the trajectories of adverse genetic influences. Intervention models which take into account the multitude of pathways by which genetic characteristics of a child may in turn impact parenting and family processes will assist in the refinement of effective interventions (Reiss & Leve, 2007). Moreover, identifying polymorphisms associated with externalizing disorders in adolescence and adulthood, as well as their behavioral presentation in toddlerhood and childhood (prior to the onset of maladaptive behavior), will help in determining at what age and in what ways to intervene and subsequently reduce the risk of the development of psychopathology. Of course, the question remains whether childhood psychopathology can be prevented by helping parents, teachers, and clinicians respond in certain ways to heritable evocative characteristics and genetically influenced behaviors. It seems likely that quantitative and molecular genetic designs will assist in this process.

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4

Process in Genetic Counseling: Considerations for Children and Their Families

JULIANNE M. O'DANIEL and ALLYN MCCONKIE-ROSELL

INTRODUCTION

The clinical variability seen in a single, inherited genetic condition is equally matched by the variability of the individual, as well as the family's response to it (O'Daniel & McConkie-Rosell, 2006). As the practice of medicine evolves beyond single gene and chromosomal disorders to include genomics, this variability is magnified many times over. Medical genomics involves the incorporation of risk associations, which are most often based on the analysis of combinations of multiple genetic variants. Patients, thus, may receive risk estimates (rather than genetic diagnoses) for a range of health conditions and states including adverse drug response and cancer recurrence. Although the magnitude and heritability of risk varies significantly between medical genetics and genomics, the basic tenets of genetic counseling can still apply.

Genetic counseling is a dynamic process that has more recently been defined as helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. This process integrates the following:

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- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources, and research
- Counseling to promote informed choices and adaptation to the risk or condition (National Society of Genetic Counselors' Definition Task Force Resta et al., 2006, p. 77)

One of the major objectives of genetic counseling is to facilitate adaptive coping through interventions designed to provide families with the knowledge, skills, and resilient self-beliefs required to cope, adjust, and affect control over their lives (McConkie-Rosell & Sullivan, 1999).

When a child is the focus of the genetic counseling, it is important to consider the developmental concerns of the child as well as the adjustment of the family. Just as children grow and change, so too does the meaning and utilization of the genetic information available to both the child and the family (McConkie-Rosell & O'Daniel, 2007). Like the clinician, parents may also be concerned about the effect the genetic information will have on their own or others' perceptions of the child and on the child's ability to understand and positively utilize the information at an appropriate time in the future. This is especially true in the case of genetics and genomics where information is learned about individuals when they are a child and which may not hold personal health implications until later on in adulthood.

The purpose of this chapter is to describe the unique environment of genetic and genomic risk information and testing in children and their families and the processes of genetic counseling to help guide families through it. Although most of the research and examples cited herein are drawn from medical genetics, the concepts and themes are very relevant in the application of genomics to broader health-related concerns.

ROLE OF GENETIC COUNSELING

The primary purpose of genetic counseling for children and their families is to facilitate familial coping and adjustment to the genetic risk and testing information. Much of the research on the emotional response, health behaviors, and uptake of a genetic test has focused on individuals and an individual response to genetic information about single gene or chromosomal disorders (Sorensen & Botkin, 2003). By its very nature, however, genetics involves families. In order to construct a counseling approach tailored to the needs of the family, genetic counselors must first seek to understand the personal meaning that the genetic information may have for the family as well as the unique family dynamics that will affect the incorporation and response to the genetic information. This is frequently done within the purview of a structured medical genetics session.

Structure of Medical Genetics Counseling Sessions

The typical components of a genetic counseling session(s) include (1) contracting; (2) collection/review of family and medical history; (3) discussion of clinical suspicion and findings; and (4) discussion/formulation of the evaluation, diagnostic, or follow-up plan.

Contracting is the process of developing a joint agenda that merges specific items the counselor wishes to address with those of the patient and family. This process is meant to fully acknowledge that each group may desire and require different information (Michie et al., 1998; Wang, Gonzalez, & Merajver, 2004). Michie and colleagues (1997) suggest that the majority of patient expectations fall into one of five categories: information, explanation, reassurance, advice, and help in making decisions. Further, these expectations are likely to shift based upon where the patient may be in the genetic evaluation process (e.g., initial consultation, pre-testing, post-testing, follow-up with or without known diagnosis) (Wang et al., 2004). Initiating an open and inclusive dialogue is critical to establishing and building trust with the patient and family. This relationship is essential to the necessary collection of private family health information and the intricately personal attitudes, perceptions, and expectations the family may have.

Through the collection of family medical histories the genetic counselor is afforded the opportunity to explore the family's experience with the disease or clinical indication including the severity and perceived burden of the disease, as well as beliefs regarding the transmission of disease within the family including who is or is not at risk (Bennett, Hampel, Mandell, & Marks, 2003). Misunderstandings and misperceptions can be brought to light and addressed. Through this process of family-centered discussion, the counseling will also elicit information about emotional relationships which are crucial to the dissemination of genetic risk information to at-risk family members.

The assimilated "family knowledge" including family health beliefs and experiences is incorporated into the counselor's dialogue, informing the discussions regarding the clinical suspicion and ultimately developing a plan that meets and addresses the agendas of the patient and family as well as the genetics medical team. This intentional process aims to link the new genetic information back to the family experience and expectations, thus increasing the personal relevance of the genetic information for the patient and family.

The structural framework of a genetic counseling session is thus highly information focused – both in the elicitation and the exchange of information. Beyond fulfilling the immediate medical need, this informational exchange and the manner in which it is performed are useful tools to establish a framework for developing relationships with the patient and family (McConkie-Rosell & O'Daniel, 2007). Based on this relationship, genetic-related beliefs relevant to health and coping behaviors, such as attached personal and familial meaning of the genetic information, may be uncovered. Elucidating these beliefs may prove critical to the integration of preventative health plans based upon, or reinforced by, genomic risk information.

Comprehension and Family Meaning of Genetic Health Information

Genetic, and certainly genomic information, can be exceedingly complex as it incorporates multiple layers of information about risk and/or diagnosis, inheritance, and management strategies. For many patients and families, not only is the information presented in unfamiliar terms, but it may also be framed by the anxiety that led to the genetic/genomic evaluation in the first place. Thus, special care needs to be given to word choice as the phrasing may be repeated throughout the family and influence understanding and response to the information. Genetics concepts are introduced and explained in an appropriate manner recognizing that some terms have become associated with negative and/or incorrect connotations in the popular media such as "mutation," "syndrome," or even "DNA test" (Bates, 2005; Bates, Lynch, Bevan, & Condit, 2005; Lanie et al., 2004; McConkie-Rosell & O'Daniel, 2007; Silva, 2005). It may also be important to distinguish different levels of risk. With single gene disorders, this may include personal risks to develop various symptoms related to a diagnosis as well as the risk for a child to be affected. Genomic health risks may be based upon an a priori, "average individual" risk, which is modified by the inclusion of additional genetic risk factors. Words like "increased," "decreased," "at risk," "high," and "low" all have very different meanings to each individual. To aid and promote patient and family understanding, genetic counseling will often incorporate educational strategies such as visual aids or conceptual analogies using familiar examples from the family's environment.

Beyond an understanding of the factual science and risk information, comprehension of the genetic information will be informed by how the information relates to the patient as an individual as well as a member of their family (O'Daniel & McConkie-Rosell, 2006). Numerous and diverse factors go into the construction of meaning such as the motivation for an evaluation, perceptions of disease and/or risk severity, and beliefs and/or misbeliefs regarding inheritance and causality. Exploration of underlying health and genetic beliefs is essential to understanding what the new genetic or genomic information may actually mean to the patient and family and thus what they will remember, as well as how and whether they will apply the information to their life. There may be family stories that account for family-specific inheritance patterns which are used to support a believed genetic status (Fanos & Gatti, 1999; Fanos & Johnson, 1995). It is not uncommon for families to discuss health behaviors that they believe may have influenced the expression of the disorder (Walter, Emery, Braithwaite, & Marteau, 2004). These family stories may also influence the child's perceptions of the disorder and its personal impact.

Genetic counseling's use of familial knowledge and experiences to aid learning is not a novel strategy for families. For example, interactions between parents and children in a science museum revealed that parents frequently provided an experiential context to learning by connecting the new scientific information to previous family experiences and shared knowledge (Crowley & Jacobs, 2002). Thus, just as genetic counseling dialogue is informed by "family knowledge," so too, may families build

upon unique family and cultural experiences when attempting to interpret and provide meaning for new genetic or genomic information.

The interpreted meaning of the disorder within the family is a critical component of the family response (Boss, 1988). In a review of the literature, Peterson (2005) concluded that the family response to a genetic diagnosis is not only influenced by factual knowledge of mutational status (e.g., mutation positive, carrier, non-carrier), but also by the order of being diagnosed in the family (e.g., first to be diagnosed) and the dynamic of family emotional support which, in the case of children, is initiated by their parents' reaction. Research on coping behaviors supports the idea that children are influenced by how their parents manage stressful situations (McKernon et al., 2001; Miller, Kliewer, Hepworth, & Sandler, 1994).

Beyond the nuclear family, personal and family meaning may be further framed by ethnic and cultural influences stemming from the communities with which they identify (Bates, 2005; Bates et al., 2005; Brunk, 2006; Catz et al., 2005; Cunningham-Burley, 2006). Examples include groups defined by religious or political beliefs as well as the socioeconomic and demographic characteristics of their geographic community. Current societies are highly diverse with different experiential influences and attitudes that can change over time. Discussions of genetic and genomic health information should acknowledge, and be responsive to, these differences (Cunningham-Burley, 2006; Gottweis, 2002; van der Sanden & Meijan, 2008; Wynne, 2006).

In summary, the educational process of genetic counseling aims to promote comprehension of genetics/genomics knowledge for families. Ideally, this knowledge should not only incorporate the conceptual understanding of the science and health implications but also be consistent with personal and family beliefs and attitudes (Wang et al., 2004). By employing an active exchange of knowledge and perceptions between the counselor and the patient/family, genetic counseling aims to achieve a "reciprocal understanding" of the factual information framed by the unique family meaning applied to that information.

Intrafamilial Relationships and Communication Dynamics

Comprehension of the genetic or genomic information is intricately linked to what, and with whom, information is shared within a family. Family communication is not only central to a functioning family system but also implicit in clinical genetics (Peterson, 2005). Communication of complex and potentially emotionally upsetting genetic or genomic information can be a difficult process. How and if it is disseminated within a family may be based upon a number of factors including:

- Initial comprehension of the information
- Personal meaning and importance attributed to the information
- Assessment of the target family member's risk
- Perception of treatment or prevention options
- Gender of the communicator

- Emotional closeness to the family member
- Predicted receptivity to the information (Gaff et al., 2007; Wilson et al., 2004)

Within families, there are primary sources and directions of communication. In a study of families affected by hereditary nonpolyposis colon cancer, the communication patterns were described as generally following the norms for conveying nonurgent news in the family. However, the index case (first to be tested/diagnosed) for the family was noted to both actively inform and persuade other members to seek counseling (Peterson et al., 2003). This responsibility "to tell" others has been seen in studies of numerous conditions (Gaff et al., 2007; McConkie-Rosell et al., 1995; Wilson et al., 2004). Whoever disseminates the information should be an individual who is known to the family and considered a trusted source (McConkie-Rosell et al., 1995). Thus, beyond a discussion of who in the family is at risk, it is essential for genetic counseling providers to elucidate the family communication dynamics and facilitate accurate sharing of pertinent information.

Beyond the simple sharing of knowledge and educating members, communication of genetic information within a family may also serve to elicit emotional and social support for coping (Duncan et al., 2008; Gaff et al., 2007; Peterson, 2005). Just as family dynamics affect communication, families may actually adjust their systems in response to new genetic information (Peterson, 2005). Sobel and Cowan (2003) found that families would either distance themselves or increase connections when trying to cope with positive predictive testing information about Huntington disease. When the information is interpreted as significantly threatening or stigmatizing, families may choose to withhold information. The act of withholding genetic information from family members may reflect efforts to protect an individual (often a child) or the public family image (Brown-Smith, 1998; Wilson et al., 2004). Conversely, family communication patterns are also affected when a condition is perceived as less serious or stigmatizing and for which there are treatments (Holt, 2006). Additional barriers to communication have been reported as a lack of familiarity or emotional closeness with a relative such that they would not typically exchange personal information, or when the genetic information is of a more ambiguous or uncertain nature (Gaff et al., 2007; Wilson et al., 2004) (Table 1).

Recognizing numerous possible barriers, practical tools to aid in the dissemination of information are often incorporated into the genetic counseling. Examples include family letters and/or fact sheets written in lay language that may address the genetic or genomic concern using either specific family information or broad but relevant terms. Such documents can provide contact information for the medical specialist who can answer additional questions and/or for clinics located closer to either the patient or the distant family members.

Further, when considering family communication, it is important to take into account that the term "family" may or may not be defined by biological relationships (Finkler, Skrzynia, & Evans, 2003; Gaff et al., 2007;

Table 1. Questions That May Be Explored with the Family to Facilitate Communication

Questions that may be explored with the family to facilitate communication include

- What is the family's personal experience with the disorder?
- What are the family's values and beliefs related to the genetic diagnosis and how do these influence the family identity?
- How as a family are they managing with the genetic diagnosis?
- What are the family's rules and role assignments?

1. Who communicates important information within the family?
2. Are there generational differences in how information is discussed within the family?
3. Are there unwritten rules about what can and cannot be discussed?
4. Who gets to make decisions and how are they made?
5. How do the parents view their role in relationship to their children?

(McConkie-Rosell & Spiridigliozzi, 2004)

Peterson, 2005; Wilson et al., 2004). While the biological ties may be the focus for discussing genetic risks, it is important to recognize and include the pertinent social bonds within the family unit. These additional connections may be just as or more important to coping with and communicating genetic information. Given the great diversity of families, genetic counseling aims to utilize distinct, tailored approaches to best facilitate each situation (Gaff et al., 2007).

Empowering Families

When genetic or genomic information is new to the family, and particularly if it is perceived as threatening or complex, the family may initially rely more on the genetic counselor, physicians, and/or other health professionals for guidance in decision making regarding treatment, testing, and other measures (McConkie-Rosell & O'Daniel, 2007; Read, 2000). During this time, families' informational needs may focus on learning the facts about the diagnosis (Starke & Moller, 2002). Indeed, for some families, being able to simply answer questions posed by health professionals, relatives, and friends can be an important first step toward gaining control over the information and the condition (McConkie-Rosell & O'Daniel, 2007). However, families also have tremendous strengths and resilience to cope with potentially threatening genetic or genomic risk information (Boss, 1988). By exploring family beliefs and dynamics, genetic counseling can help to tap into those strengths.

In the case of children and their families, genetic counseling actively partners with patients and their families to enable them to positively incorporate genetic information, promoting self-efficacy and family efficacy. Inclusionary discussion with the family can help empower them to take control of the genetic information and to apply it in a meaningful way (McConkie-Rosell & O'Daniel, 2007). This approach is inclusive of multiple family members as appropriate including the child, siblings, parents, and extended relatives.

SPECIAL CONSIDERATIONS FOR CHILDREN

Genetic and Genomic Testing

A significant motivating reason to seek genetic testing is concern for children. Families frequently wish to determine if a child is at risk for a health or reproductive concern (Esplen et al., 2001; Wang et al., 2004). Thus, genetic or genomic risk information for the child may be introduced through the testing of a parent, another relative, or the child themselves. Unlike genetic testing, genomic testing is almost always concerned with multiple genetic variants that have been statistically associated with risk probabilities. For example, children could be tested to learn whether they have an increased risk to develop various health conditions or an increased or decreased chance of responding favorably or adversely to a medication and not to determine if they have "the genetic change" for a specific single gene disorder. Even if the probability for the risk is high (say, greater than 50%), current genomic tests are not diagnostic.

Genetic testing, on the other hand, can be divided into three general categories: diagnostic, increased risk, and carrier testing (O'Daniel & McConkie-Rosell, 2006) with each type of test resulting in different levels and certainties of risk. Diagnostic genetic testing refers to testing in which the genetic change has been linked with certainty to a specific genetic disorder (e.g., changes within the FBN1 gene and Marfan syndrome). As such, it can be performed either before (presymptomatic) or after (symptomatic) the onset of symptoms associated with the disorder. Symptomatic testing in children can be motivated by the desire to elucidate the cause of symptoms or to confirm a suspected diagnosis and is part of routine medical care. Presymptomatic testing is typically motivated by the existence of a family history of a genetic disorder and provides individuals the opportunity to learn whether or not they have inherited a genetic change that will cause a major health problem later in life (e.g., Huntington disease which often develops after age 40 or familial adenomatous polyposis which often develops in early adolescence).

Increased risk genetic testing is unique from genomic testing in that the test determines whether or not there is a function altering genetic change within a specific "disease gene(s)." Having the gene change is not diagnostic of the disorder, but significantly increases the individual's chance to develop symptoms at some point in their lives. In addition, the person can pass the "disease gene" onto future children regardless of whether they themselves ever develop symptoms. An example of this type of testing is the BRCA1 and BRCA2 genes in which functional genetic changes may be associated with an up to 80% chance of developing breast cancer if the person is female.

Carrier testing may be performed in the case of an autosomal recessive genetic disorder such as cystic fibrosis or sickle-cell disease. The purpose of the test is to determine if a person has an altered copy of a gene that could be passed onto children. To be affected by an autosomal recessive disorder, a child must inherit an altered gene copy from each parent.

Carriers are at risk to have an affected child, but do not themselves have the genetic disorder.

When considering genetic or genomic information for children, the manner in which the risk information is learned is also important to consider. The information can be either intentional (the test is specifically being requested) or an incidental finding related to routine, or otherwise indicated, medical evaluation such as newborn screening or prenatal ultrasound and/or serum screening (McConkie-Rosell & Spiridigliozzi, 2004).

Ethical Concerns About Testing

Historically, the discussion of children related to genetic risk has focused on whether or not to offer testing for a specific genetic disorder. Therefore, a discussion of genetic counseling focused on genetic risk to minor children is incomplete without considering the current guidelines for genetic testing in childhood. Genetic testing in minor children presents a complex ethical and social concern. Current practice guidelines regarding the timing of testing for genetic disorders in children and adolescents emphasize a respect for the autonomy of the minor, as well as concerns for the minor's psychosocial well-being including harm to the developing self-concept, stigmatization or discrimination, and altered family relationships (American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors, 1995; Andrews, 1994; Clarke, 1994; Fryer, 2000; Ross & Moon, 2000; Wertz, Fanos, & Reilly, 1994) (Table 2).

Table 2. Discussion Areas in the Decision-Making Process About Genetic Testing in Childhood

Discussion areas in the decision-making process about genetic testing in childhood:

1. The right of parents to request testing
2. The maturity of the child and his/her ability to participate in the decision-making process
3. The limitation of the child's future right to make an autonomous decision
4. The loss of the confidentiality of the child's genetic status
5. The possible stigmatization of the child because of his/her test result

(Clarke, 1998)

A review of current published practice guidelines for consensus on both carrier testing and presymptomatic testing (Pascal Borry, Fryns, Schotsmans, & Dierickx, 2006) found that there was general agreement in the guidelines that carrier testing should be postponed until the child is old enough to give informed consent. There were also three areas of disagreement or inconsistency involving (1) the duty to recontact to ensure that the child is informed as an adult, (2) acknowledgment that not offering testing could have negative consequences for the child if parents felt this information was strongly desired, and (3) whether genetic status

learned incidentally through newborn screening or prenatally should be disclosed to parents.

There is greater agreement in the guidelines addressing presymptomatic genetic testing with consensus that the primary reason for offering testing for the child is to provide an immediate and relevant medical benefit to the child (Borry, Stultiens, Nys, Cassiman, & Dierickx, 2006). The definition and level of evidence required to support the potential health benefit, however, is left to interpretation. The potential health benefits are weighed against the potential harm of having a genetic or genomic test including psychological (e.g., depression, negative self-esteem), economic (e.g., increased health-care costs), and physical harm resulting from increased preventative or screening medical procedures (e.g., imaging studies). This weighing of potentials (harms associated with learning risk information versus medical/health benefit) is particularly relevant in the case of genomic health risk testing in which the genomic information is not diagnostic. In these cases, the prevention actions are often based on diet and lifestyle behavior changes and the majority of conditions have adult onset of symptoms.

Although the focus of much of the debate about genetic testing in children has been on the potential harm, some have raised the possibility that not addressing the issue of genetic testing may be fraught with just as many concerns (Binedell, Solden, Scourfield, & Harper, 1996; Elger & Harding, 2000; Michie & Marteau, 1996). Possible benefits include helping children adjust to the information before they need to make choices about marriage and reproduction, enhancing communication, and resolving parental concerns about carrier status (Michie & Marteau, 1996; Richards, 1998). Elger and Harding (2000) suggest that "granting choice and control has a positive value for adolescents" and "respecting an adolescent's autonomous choice concerning genetic testing has positive consequences for self-esteem and psychological health" (p 118). Robertson and Savulescu (2001) have proposed that providing genetic information to children gives them a different, though not necessarily worse, reality.

Families may be caught between different medical views and determining the best approach for their own child may be difficult. Studies have shown that there is a strong sense of a parental right to decide when to inform their children of the genetic risk and when to have carrier testing done (McConkie-Rosell, Spiridigliozzi, Iafolla, Tarleton, & Lachiewicz, 1997; McConkie-Rosell et al., 1999). This is often coupled with a responsibility to help their children adjust to this information and to provide essential genetic information at the most appropriate time (McConkie-Rosell et al., 1997; McConkie-Rosell, Spiridigliozzi, Dawson, Sullivan, & Lachiewicz, 2002). The complexity and ultimate concern for the well-being of children inherent in this issue is apparent in Hamann and colleagues' (2000) finding that although a majority of parents supported testing minors for a breast cancer susceptibility gene, less than 20% felt they would actually test their *own* child.

Parental decision making about when, how, and if to inform children about genetic risk has been found to be influenced by the nature of the disease, treatment or options to reduce risk, pattern of family

communication, and coping response of the family (Forrest et al., 2003; Holt, 2006; Peterson, 2005; Wilson et al., 2004). The pattern of family communication in regard to genetic risk information has been described as a deliberative process in which (1) risk is interpreted and personalized; (2) the vulnerability and receptivity of the family member is assessed; (3) decisions are made about what will be conveyed; and (4) a good time to inform is identified (Gaff et al., 2007). Thus, parents may be faced with not only concerns regarding a child's ability to understand genetic information, emotionally manage it, and apply it when needed in their lives but may also have concerns regarding their own ability to understand the implications of the genetic or genomic information and consequently provide accurate information for their child. Forrest and colleagues (2003) found that parental confidence in ability to inform was correlated with degree of certainty about the meaning of the information.

Tercyak and colleagues (2002) found that the age of the child was the primary factor that determined if genetic testing information for hereditary breast cancer was disclosed to minor children. Holt (2006) reported two distinct opinions regarding family communication about genetic risk for Huntington disease. The adult children in her study expressed a preference to have learned about Huntington disease and their genetic risk early in life, preferably through a parent. The parents with Huntington disease in the family, however, felt genetic information needed to be discussed with children at key time points when there was a direct need for the information, such as when their child was getting married and/or considering having children of their own (Holt, 2006).

In a study of adolescent girls and young women from families with fragile X syndrome, all recommended teen years or younger as a preferred age to learn about either the inheritance of fragile X syndrome or their own carrier status (Wehbe, Spiridigliozzi, Melvin, & McConkie-Rosell, 2009). The girls in this study frequently recommended a staged approach to learning genetic risk information suggesting the information should be normalized and given with a large dose of reassurance. They also emphasized the importance of being provided with the information early on in order to help them adjust to it and to better understand their families and themselves.

Although the ethical debate about genetic and genomic testing in children is unresolved, families are currently managing genetic information and dealing with the implications for their children. When considering genetic or genomic testing, both the parent and child's desire for the information and the impact of the information in terms of benefits and harms should be explored. Once information is learned, parents are then faced with difficult questions regarding when and how to provide genetic risk information in a manner that is positive for their children.

Considerations for Communicating Genetic and Genomic Information to Children

Although there is very limited research on the effect of genetic information on minor children (and none regarding genomic information),

patterns are beginning to emerge that can help to inform genetic counseling as well as areas of future research. Communicating genetic risk information to children is a process which, for some families, may occur over many years. Genetic counseling aims to facilitate this process by tailoring an informational approach that is sensitive to the family's needs at a given point in the process while anticipating future needs. Some of the barriers to informing children about genetic risk are parental concerns about (1) potential harm to their child's self-concept, (2) psychosocial adjustment to the information, (3) worry over providing the correct information, and (4) identifying the best time to disclose information to facilitate coping and adjustment in their child (Tercyak, Hughes et al., 2001; Tercyak et al., 2007). Further, McConkie-Rosell and colleagues (2009) identified three ways in which children in families affected by fragile X syndrome learned genetic information: (1) open discussion with adult relatives, (2) limited discussion in response to specific questions only, and (3) indirect or overheard information.

Children overhear conversations being held by adults both at home and in the medical clinic and may begin drawing their own conclusions. They will also overhear conversations among family members going through testing themselves including discussions of who is and who is not a carrier in the family. Tercyak and colleagues (2001) found that children in families diagnosed with breast cancer often learned about the genetic risk through overhearing conversations of those family members who were affected or who were undergoing testing. Therefore, it is important for parents to consider not only directed conversation but also what the child may indirectly, and potentially incorrectly learn through the family environment, the family response to the diagnosis, and how and what information is being discussed among adults.

Along similar lines, Koopman and colleagues (2004) found that children learn as much from what they see their parents do and how they experience their families reacting than from what is simply said. Children may not understand the implications of the diagnosis, but may focus on the emotion with which it is presented. Fivush (1998) found that children are affected not only by an event as it is occurring, but also by how it is discussed by family members afterward.

Parents may intentionally withhold information in an attempt to keep a "family secret." While family secrets can start with a protective purpose, once revealed a secret can have negative, unintended consequences (Brown-Smith, 1998). Children, especially adolescents, may react with anger and a sense of being betrayed (Wehbe, Spiridigliozzi, Melvin, & McConkie-Rosell, 2009). In studies of parental concerns about providing genetic risk information to children, the need to protect children from possibly upsetting or emotionally difficult information is a major reason why children may not be told (Holt, 2006; Tercyak et al., 2007; Tercyak, Peshkin, Streisand, & Lerman, 2001). The tension between a desire to protect a child from difficult information and the desire to help a child adjust to that information is not unique to genetic disorders. Hahan and Craf-Rosenberg (2002) found similar concerns about disclosing biological origins to children when donor egg and/or sperm were used. The burden

of having to "live a lie" and concern about harm to parent/child trust were the major reasons identified for choosing to disclose.

Children are not adults and may have a very different interpretation or understanding of the health information that is either discussed with them or that they overhear being discussed by their parents. Children as young as preschool age are capable of understanding that some illnesses can be "caught" and others can "run" in families when presented with appropriate cues (Raman & Gelman, 2005). They may also have questions of their own which are important to address, because as with any medical disorder there are often misunderstandings (Koopman et al., 2004). Finding the right words, however, is not a matter of simply using smaller words.

For example, according to Piaget's theory of cognitive development, children aged 7–8 years are able to think logically and consistently about real and concrete features of their world. However, it is not until age 10 or 11 years that children can think hypothetically and abstractly and are able to speculate about possibilities (Berger & Thompson, 1995). Given the mathematical and conceptual complexity of risk, it is important to consider the developmental stage and personal experiences of the child. Exploration of the child's perception can not only help parents find the best time to communicate genetic or genomic information, but can also provide insight into how this information can be managed for a child.

Parents have expressed a need for help in deciding what was best for their family (Hahan & Craf-Rosenberg, 2002). An important role for the genetic counselor is helping families to understand and then practice talking about the genetic information, attempting to anticipate responses as well as questions the child may have. Careful planning with the parents about what the child knows and understands about the disorder can help to prevent misunderstandings.

Table 3. Questions That Might Be Explored with the Parents

Questions that might be explored with the parents include

- How old is the child(ren) in the family, currently?
- What are the implications of learning the information now versus a staged approach in the future?
- What is their personal experience with the particular disorder or health concern?
- How as a family are they managing with the genetic diagnosis or information?
- What do they understand about the inheritance, morbidity, mortality, and medical management indicated by the genetic/genomic information?
- What do they understand about the implications of the information for themselves and their family?
- How has the family responded to the information?
- What do they do to manage negative emotional responses?
- What have they told/said to their child(ren) about the genetic/genomic information and implications for the family?
- What do they think their child(ren) understands about the genetic/genomic information?
- How do they think their child(ren) have interpreted this information?

(McConkie-Rosell & Spiridigliozzi, 2004)

Just as a staged approach to providing the information to children may be helpful, a staged approach to genetic counseling may also be appropriate. Multiple genetic counseling sessions, planned over several years, allow for the opportunity to address misinformation and provide new relevant information including medical, diet, behavior, or educational interventions as well as an opportunity to manage the maturing emotional responses to the genetic or genomic information (McConkie-Rosell & O'Daniel, 2007). Additionally, allowing for future visits enables the genetic counselor to address the child's own future concerns such as the availability of new technologies and treatments or planning a family (Table 3).

INCREASING THE COMPLEXITY: INTEGRATING GENOMIC RISK INFORMATION

The field of medical genetics has continuously evolved over recent decades to incorporate advances in knowledge, treatment, and testing technologies. Examples include the emergence of genetic services for inherited cancer syndromes, expanded scope and guidelines for prenatal screening, improving artificial reproductive technologies and preimplantation genetic diagnosis, and expanded newborn screening and testing. Following the completion of the draft sequence of the human genome, the pace of discovery in the field of genetics and genomics has rapidly escalated. The ensuing advances in knowledge and technology have been described as revolutionary for both science and society. Genomic medicine and the capability to analyze whole genomes and harness that knowledge for improving health and disease "is a natural extension of genetic medicine" (p. 151) (Guttmacher, Porteous, & McInerney, 2007). Indeed, the era of genomics holds tremendous promise for the entire field of medicine, potentially transforming the very manner in which health and disease are considered (Bentley, 2004; Cheng, Cohn, & Dover, 2008; Chesney, Friedman, Kanto, Bonita, & Stull, 2002; Willard, Angrist, & Ginsburg, 2005).

Genomic Testing and Risk Information for Children and Families

This shift in focus from diagnostic to probabilistic risk information presents great opportunity and challenge especially in regard to genomic testing and risk information for children. Genetic and genomic testing for families and children in the era of genomic medicine has been predicted to primarily involve four areas: (1) expanded, universal newborn screening, (2) targeted, diagnostic testing in common, complex conditions, (3) predictive screening of genetic health predispositions, and (4) pharmacogenetic testing for variation in drug response (Cheng et al., 2008). Research is already revealing evidence of gene–environmental interactions very early in development that have implications for emerging disease

in the neonate (Cotton, Ginsburg, Goldberg, & Speer, 2006), the child (Emonts et al., 2007), and the adult (Eriksson, 2007), thus, raising the question of immediate intervention for immediate and/or future benefits.

Genomic-guided medicine hopes to afford healthy patients the opportunity to undergo screening tests for risk assessment of a variety of common health conditions and drug reactions about which they may have no prior history or current symptoms and which may not occur for some time. Clinicians who care for children and families will have the first opportunity to predict gene-based risks and thus intercede in the possible progression of disorders through family-centered treatment and care (Cheng et al., 2008).

New Challenges

At this early stage, the potential impact of genomic risk information for children and families remains largely unexplored. Here we describe four potential issues that warrant additional research: patient attitudes and perspectives, adoption of health behavior change, reinterpretation, and incidental or unintended findings.

It is generally felt that genomic information will likely not carry the same potential for social stigma as traditional medical genetic diagnoses and/or risks. In comparison to traditional genetic disease, genomic risks will be smaller in magnitude, pertain to more common, potentially well-recognized categories of disease, and most likely infer some level of "increased risk" for everyone. The fact remains, however, that this information is DNA based and with the label of being "genetic" may carry similar weight to genetic diagnostic or risk information. The public's perceptions and attitudes toward genomic risk information will substantially influence the uptake and successful integration of these new tests into health care. Whether patients and families will associate genomic risks with preconceived notions of genetic disease remains to be seen.

The medical value of the genomic risk information to prevent disease or reduce disease severity will depend on the likelihood of individuals to modify lifestyle and health behaviors. As most families have no prior experience with genomic information, the initial impact will be influenced by preconceived ideas about genetic information framed by personal, family, and community values and experiences. The data appear to be mixed regarding whether receiving genetic risk information can motivate behavioral change (Marteau & Weinman, 2006; Phillips et al., 2006; Frosch, Mello, & Lerman, 2005; Peshkin et al. 2002). Understanding the factors that are influential in behavior modification based on the varying probabilities of genetic and new genomic information will be important in determining the impact of this information to prevent disease (Marteau & Weinman, 2006).

Green and Botkin (2003) suggested that the introduction of predictive genetic testing into health care should not, in and of itself, lead to new-found ethical dilemmas, but should be carefully assessed for the added benefit and harm predictive testing could have for the patient (Green & Botkin, 2003). This same logic should be applied to genomic

testing. Unique to genetic and genomic testing as compared to other medical tests and screens, however, is the fact that aside from tissue-specific testing (e.g., testing of a tumor), a result will not change, remaining constant throughout an individual's lifetime. Because of this, genomic test information may present a new perspective for an old dilemma: duty to recontact.

Although the genomic test results will not change, the medical interpretation of what the result means will change as the field advances and our knowledge continues to expand. Routine "reinterpretation" of genomic health risks will be essential to ensure health plans are based on accurate information. When a reinterpretation is necessary and how it might best be handled are concerns that warrant exploration (Shirts & Parker, 2008).

Another complication of genomic risk information is that many DNA changes (e.g., single nucleotide polymorphisms (SNPs)) may in fact be linked to more than one health risk or state. In a study of variants significantly associated with pharmacogenetic indications, 23 of 42 (55%) had also been reported to be associated with at least one if not two or three common diseases (Goldstein, Tate, & Sisodiya, 2003). Individuals could be faced with learning incidental or unintended information about disease risks for which they had not sought testing at variable times in the future. There is currently no consensus or guide as to when new information about genomic risks should be shared with a patient or by whom.

Counseling About Genomic Health Information

As in the case of medical genetic information, families will need to be guided about how best to balance the desire and need for information (Peterson, 2005). Given the broader, potentially universal application for predictive genetic/genomic testing, the role of counseling as it relates to the incorporation of genomic risk information into preventative health plans will need to expand beyond traditionally trained and certified genetic counselors and be adopted by other health-care providers (Chesney et al., 2002) or via other formats. Due to the complexity of genomic health risk information, however, a strategy for genetic specialist consultation or referral should be established to ensure families receive accurate and appropriate support and guidance.

To have the greatest preemptive effect and promote the greatest access to these new tests, a natural choice for delivery is primary care providers (PCPs). Due to their longer term role in the overall health of patients and families, PCPs are in a unique positions to offer truly personal medicine based upon the provider–patient relationship and not just the application of new technologies (Burke & Psaty, 2007). As the ultimate goal for many genomic tests will be long-term health status, counseling strategies for patients, especially children and families, will need to incorporate a long-range approach. The decision to undergo genomic testing will simply be the first of multiple decisions that the patient and family will need to make (Wang et al., 2004). It is essential to develop a strategy of educational

programs for these providers that can offer not only conceptual grounding but also a means of incorporating new knowledge disseminating from the rapid pace of research (Chesney et al., 2002; Goldstein et al., 2003; Greendale & Pyeritz, 2001; Guttmacher et al., 2007; Peterson, 2005).

CONCLUSION

Just as technology is evolving, so must our concept of the role of genetic counseling in how genetic and genomic information is communicated to and within the family. When the focus is on the minor child in the family, consideration must be made of the age of the child, developmental stage, implications for the present and the future, family culture, coping resources, and interpretive meaning of the information to the family. Genetic counseling for families faced with decisions about how best to talk with their children not only must consider the ethical issues but also must focus on how to help families cope with sometimes difficult information and to incorporate that information in a positive manner.

As health care progresses toward incorporation of genomic medicine, the informational and health needs of children and their families should be weighed. We must consider how children perceive genomic risk information and changes to health risk perceptions. Approaches to informing them about health risks which can result in the adoption of positive health behaviors and healthy self-concept need to be explored, interventions developed, and their effectiveness evaluated. As the concept of genetics for many families moves from single genes and connotations of genetic disease, to overlapping risk factors, new strategies for thinking about and managing information in the family may be required. Building upon genetic counseling fundamentals, the process of counseling about "genomic" health risks may utilize similar approaches to explore what this new information may mean for the child and his/her family and to guide incorporation of this information into proactive health planning.

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5

Genomics and the Family: Integrative Frameworks

MARCIA VAN RIPER

INTRODUCTION

Recent advances in genetics and genomics are having a profound impact on our understanding of the biological underpinnings of health and human development (Cutfield, Hofman, Michell, & Morison, 2007; Grigorenko, 2009; Obradovic & Boyce, 2009). In addition, recognition that many of the health conditions seen in childhood, both rare (e.g., sickle cell disease) and common (e.g., asthma), are influenced by a complex interplay between genetic and environmental factors has contributed to noteworthy changes in the diagnosis, treatment, and prevention of many childhood conditions (Buchanan et al., 2009; McBride & Guttmacher, 2009; Moeschler, 2008; Moore, Khoury, & Bradley, 2005; Rutter, Moffitt, & Caspi, 2006). Moreover, there has been growing interest in how families influence and are influenced by the way in which individuals adapt to being tested for and living with a genetic condition (McDaniel & Campbell, 1999; Feetham & Thomson, 2006; Rolland, 1999; Sorenson & Botkin, 2003; Tercyak, 2009; Van Riper, 2005; Van Riper & Gallo, 2005).

The main purpose of this chapter is to demonstrate how the use of a guiding framework can help family scholars (e.g., family researchers, therapists, educators, physicians, nurses, psychologists, and genetic counselors) work more effectively with individuals and families being tested for and living with genetic conditions, especially young people. First, there is a brief discussion about the importance of theory and theorizing in this context. Next, a case study about an adolescent with sickle cell disease who sought treatment for an acute painful episode in the emergency room is presented to illustrate that living with a genetic condition is both an individual and a family experience. Then, there is an overview of individual and family factors found to influence how individuals and

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families adapt to being tested for and living with a genetic condition. After this, specific aspects of the case study are further developed to highlight which of these individual and family factors seem to have the greatest impact on how the adolescent with sickle cell disease and her family are adapting to the ongoing challenges associated with this condition (e.g., acute pain episodes and lack of awareness on the part of teachers and health-care professionals regarding how to best manage these acute pain episodes).

In the next section of the chapter, five frameworks that have been used to explain or predict how individuals and families respond to the experience of being tested for and living with a genetic condition are presented. In two of the frameworks (i.e., the Disability-Stress-Coping Model and the Transactional Coping and Stress Model), the primary focus is at the individual level, while in the other three, the primary focus is at the family level (the Resiliency Model of Stress, Adjustment, and Adaptation; the Family Management Style Framework; and the Family Systems Genetic Illness Model). Given that a main focus of this volume is on the family, the frameworks that place a greater emphasis on family are presented in greater detail. Following the presentation of these frameworks, there is discussion of how the plan of care for the adolescent with sickle cell disease and her family might differ depending on which of these five guiding frameworks is used. Finally, the chapter concludes with a summary of the key issues discussed and implications for future research.

The case study presented in this chapter is based on a family interview that was conducted as part of an ongoing program of research concerning the family experience of being tested for and living with a genetic condition (Van Riper, 2001a, 2004a, 2004b, 2005). Five family members (i.e., both parents and three of their five children) participated in the interview. The interview took place in the family home. It was recorded on a digital recorder and transcribed verbatim. Names of family members have been changed to protect confidentiality.

IMPORTANCE OF THEORY AND THEORIZING

In the first *Sourcebook on Family Theory Project* sponsored by the National Council on Family Relations, theory was defined as "a set of logically interrelated propositional statements that identify how variables are covariationally related to each other" (Burr, Hill, Nye, & Reiss, 1979, p. 17). However, in the most recent *Sourcebook of Family Theory and Research* (Bengtson, Accock, Allen, Dilworth-Anderson, & Klein, 2005), the authors decided that a simpler, more direct definition of theory was needed, so they defined theory as "an attempt to explain" (p. 5). Additionally, they described theory as "a tool to help us understand, explain, and give meaning to the data we have collected" (p. 7). Bengtson and colleagues encouraged family scholars to use the term "theorizing," which they defined as "a process of developing ideas that allow us to understand and explain our data" (p. 4). They maintain that use of the term theorizing

helps shift the focus from theory as a noun or modifier to theory as a verb. Importantly, this shift captures the notion that theory is a process, not a product.

According to Bengston, lead author of the *Sourcebook* (Bengston et al., 2005), theorizing is akin to putting together a puzzle. By itself, each piece of the puzzle is incomplete, mystifying, and confusing. Yet, in the process of trying to understand how the pieces fit together, we are often able to discern a larger and more coherent whole. Bengston went on to argue that theorizing is crucial if we want our research with families to be useful to other family scholars. When we explain and interpret our findings within explicit theories or conceptual frameworks, we help to build cumulative knowledge which, in turn, may ultimately lead to more effective interventions, well-informed policies, and solutions to real-world problems that families face. Moreover, theorizing can be highly engaging; being able to create your own puzzle rather than solving one that someone else has already solved is rewarding because it allows for creativity and flexibility in thought processes. Finally, Bengston described theories as lenses. When you observe a family through one lens, you will see their behavior accordingly. However, if you switch to another lens, you may observe something different.

It is doubtful that any single lens or conceptual framework adequately describes the complex relationships that exist among the individual and family variables that contribute to adaptation in families affected by genetic conditions. Hence, family scholars must be versatile and familiar with more than one conceptual framework. Not only will this make it easier for them to consider the wide range of issues that may be affecting individuals and families living with a genetic condition, but it will also improve their ability to think critically and in a transdisciplinary manner. Family scholars who are able to use a variety of conceptual frameworks have a better chance of noting the complexity and diversity of family processes and a better chance of understanding the intricacies of family life (Hanson & Kaakinen, 2005). In contrast, family scholars who rely upon the same framework may actually limit their possibilities for discovery and new opportunities for intervening with individuals and families affected by genetic conditions.

CASE STUDY

Jennifer is an 18-year-old Black female with sickle cell anemia who presented in the emergency department for treatment of an acute painful episode. Sickle cell anemia is the most common form of sickle cell disease. Individuals with sickle cell anemia have two abnormal hemoglobin (HBB) genes and both of these are *Hb S* genes; one of the *Hb S* genes was inherited from their mother and the other from their father. Individuals who have only inherited one *Hb S* gene are known as carriers of the sickle cell trait. The clinical manifestations of sickle cell disease in children and adolescents result primarily from hemolysis and vaso-occlusion. Common health problems associated with sickle cell anemia include

pain episodes (that are often unpredictable), delayed growth, anemia, acute chest syndrome, bacterial infections, damage to the spleen, cerebral vascular infarctions, necrosis of the femoral head, dactylitis (a painful swelling of the hands and feet), and enuresis (Wethers, 2000).

Three hours prior to going to the emergency department, Jennifer was in her family home studying for final exams when she began experiencing pain in her arms and chest. Initially she attempted to deal with the pain by drinking water, resting, and taking two tablets of Percocet (a narcotic analgesic prescribed by her primary physician). However, once it became clear that these measures were not going to be effective in relieving her pain, Jennifer asked her parents to take her to the emergency department in the community hospital located near their home.

When Jennifer, her parents, and two of her siblings arrived at the emergency department they were told, "It will be awhile before anyone can see you." Jennifer waited over 2 hours before she was taken back to the examination room. During this time, members of Jennifer's family, especially her father, became upset because Jennifer's pain level increased from 8 to 10 on a 10-point pain scale. Fortunately, Jennifer was able to fall asleep once she received intravenous fluids and a dose of morphine (a more powerful narcotic analgesic). However, shortly after Jennifer fell asleep, the physician who had prescribed the morphine woke Jennifer up to ask her about her pain level. When she told him it was still a 10, he said, "I don't understand, how can your pain level be 10 if you were able to fall asleep." According to Jennifer, "He basically accused me of being a drug addict and sent me home." Jennifer and her family ended up leaving the emergency department dissatisfied with the care she had received. Unfortunately, this was not the first time they had been dissatisfied with how physicians and other clinicians managed Jennifer's pain episodes. In fact, Jennifer's parents reported that being able to obtain high-quality care in a timely manner for Jennifer and her oldest sister Sylvia (who also has sickle cell disease) is one of their family's greatest challenges.

INDIVIDUAL AND FAMILY FACTORS THAT INFLUENCE ADAPTATION

Individual factors shown to influence adaptation in families being tested for and living with a genetic condition include demographic factors (e.g., age and gender), knowledge and attitudes (e.g., knowledge of genetic concepts and genetic testing, beliefs and expectations about risk management and disease outcomes, and previous experience with individuals and families being tested for and living with genetic conditions), interpersonal factors (e.g., temperament, problem-solving ability, and the ability to process numerical risk information), psychosocial stress (e.g., increased demands associated with the genetic condition, daily hassles, and major life events), and stress-processing factors (e.g., cognitive appraisal and coping strategies) (Brown, Doepke, & Kaslow, 1993; Hurley, Miller, Rubin, & Weinberg, 2006; Thompson & Gustafson, 1996; Thompson, Gustafson, George, & Spock, 1994; Wallander & Varni, 1998).

Family factors include sociodemographics (e.g., family size, family income, family structure and number of family members with the genetic condition), family demands (e.g., normative and nonnormative demands), dimensions of family functioning (e.g., adaptability, cohesion, family rules and hierarchy, role performance, family communication and problem solving, boundaries, family management style, and transgenerational patterns of coping across the life cycle), family appraisal (how the family as a unit views the condition or the subjective meaning they attribute to important elements of their particular situation), and family resources (e.g., strengths and capabilities of individual family members, the family working as a unit, and the community) (McDaniel, Rolland, Feetham, & Miller, 2006; Van Riper, 2000, 2005, 2007; Van Riper & Gallo, 2005). Thus, like many chronic diseases of childhood, sickle cell disease is a highly complex biopsychosocial illness that influences and is influenced by the family. These factors are further explicated below.

FACTORS THAT INFLUENCED ADAPTATION IN JENNIFER'S FAMILY

The most important individual factors influencing adaptation in Jennifer's family appear to be (1) age (i.e., age when Jennifer and Sylvia first began exhibiting symptoms of sickle cell disease), (2) knowledge and attitudes about sickle cell disease (i.e., awareness of carrier status and attitudes about life with sickle cell disease), (3) interpersonal factors (i.e., temperament and problem-solving ability), (4) psychosocial stress (i.e., increased school-related stress due to the occurrence of painful episodes and stressful interactions with teachers and health-care professionals), and (5) stress-processing factors (e.g., cognitive appraisal and coping strategies). As far as family factors, critical factors appear to be (1) family communication and problem solving, (2) family rules, (3) family appraisal, and (4) family management style. By seeking to understand the whole experience of Jennifer's genetic illness, a more comprehensive understanding of her health-related quality of life may ensue.

Jennifer did not start exhibiting symptoms of sickle cell disease until she was 16 years old. In contrast, Sylvia became symptomatic during infancy. By the time Sylvia was diagnosed with sickle cell disease at the age of 8 months she had already been hospitalized numerous times for fevers of unknown origin and ear infection. Throughout Sylvia's childhood, pain episodes were frequent and difficult to predict. The pain episodes that Jennifer experiences are different than those that Sylvia experiences. Jennifer's pain episodes are characterized by severe bone pain, while Sylvia's pain episodes are characterized by chest pain and aching in her arms. Eventually, Jennifer will most likely need a hip replacement.

Prior to Sylvia's birth, Jennifer's parents were not aware they were carriers of an *Hb S* gene. Once they became aware of they were both carriers, they decided to undergo sickle cell testing on any subsequent children. They were not interested in prenatal testing for sickle cell disease

because they did not view terminating an affected pregnancy as an acceptable option for their family. Therefore, all five of their children underwent diagnostic genetic testing for sickle cell either as a newborn or a young child; two tested positive for sickle cell disease and the remaining three are carriers.

Jennifer and Sylvia have different temperaments and different problem-solving abilities. In addition, they differ on how they respond when they have a painful episode. As far as their knowledge and attitudes about sickle cell disease, these seem to be similar. Jennifer is described as the "tough one" and she is more outspoken than Sylvia. When Jennifer is experiencing a painful episode, she wants to be left alone. In contrast, when Sylvia is experiencing a painful episode she wants someone to stay with her. As noted previously, both Jennifer and Sylvia have experienced stressful interactions with teachers and health-care professionals. In addition, they both reported experiencing school-related stress on a regular basis. This was confirmed by their parents and their sibling Carrie, who is unaffected.

When Sylvia was in the first grade, her teacher frequently questioned whether or not she was "really" having a painful episode. One time, she told Sylvia's mother that Sylvia must not have been "too sick" because she had observed her being very active in the family car. This infuriated Sylvia's mother.

Jennifer and her family members communicate openly with each other; they are not afraid to say what they think or feel. There are clear rules for how family members should behave. According to Jennifer's mother, "Education has always been a big thing in our house. If you are in this family, you are going to go to church, you are going to go to school, you are going to get a job and you are going to respect the rules of the house."

As far as how Jennifer and Sylvia manage the ongoing challenges associated with living with sickle cell disease, decisions about treatment choices are generally left up to them because "it is their life." Shortly after Sylvia's 18th birthday, a bone marrow transplant was offered as a treatment option because Sylvia's health problems were becoming more severe. Sylvia's parents allowed her to make the decision to proceed with a bone marrow transplant. Sylvia told her parents, "Either way it is going to do something. If I die, at least I will get to heaven and I won't have the pain anymore. If it cures the sickle cell, I won't have pain anymore. So, either way I won't have pain anymore." Sylvia did not end up undergoing a bone marrow transplant because her primary physician decided to first try starting her on hydroxyurea (a chemotherapy agent that had been shown to decrease the number and intensity of pain episodes in some individuals with sickle cell disease). Sylvia responded well to the hydroxyurea and she no longer needed a bone marrow transplant. In contrast, hydroxyurea has not been as beneficial for Jennifer; she did not experience a significant decrease in the number and intensity of pain episodes.

In Jennifer's family, sickle cell disease is viewed as a challenge that one can live well with and even thrive. Jennifer's parents believe their children can accomplish anything they want to accomplish. Despite having to

miss a great deal of school due to pain episodes, both Sylvia and Jennifer completed high school, found jobs they enjoy, and actively participated in school and community activities. Sylvia graduated from high school with straight A's and recently graduated from college. This picture of success is different than the picture that was painted when Sylvia was initially diagnosed. According to their mother, "The physician who told us about Sylvia's diagnosis told us all the things she would not do and said she would probably not live past 6 years old. So we treated her as if she was in an egg shell for awhile." Fortunately, the physician who treated Sylvia in the emergency department a year later responded differently. He told them, "It looks like you know what to do. Check her spleen and everything. Take her to the hospital when you think she needs to be seen. Let that girl alone. Let her go ahead. Let her do everything she can."

RISK–RESISTANCE ADAPTATION MODELS

A number of risk–resistance models have been developed to explain and predict how children adapt to chronic health conditions. The two most widely used risk–resistance models are the Disability-Stress-Coping Model (Wallander & Varni, 1989) and the Transactional Coping and Stress Model (Thompson & Gustafson, 1996; Thompson, Gill, Burback, Keith, & Kinney, 1993; Thompson et al., 1994; Thompson, Gustafson, Hamlett, & Spock, 1992). These two models have been used primarily to identify processes that contribute to adaptation in children with chronic conditions. They have both been expanded to identify processes that contribute to adjustment in mothers of children with chronic conditions as well. Moreover, Burlew (2002) developed a psychosocial assessment form guided by these two conceptual models, and Gold and colleagues (Gold, Treadwell, Weissman, & Vichinsky, 2008) expanded the Thompson model to identify processes that contribute to the psychological adjustment of siblings of children with sickle cell disease.

The Disability-Stress-Coping Model (Wallander & Varni, 1989) is based on earlier work by Pless and Pinkerton (1975), Moos and Schaefer (1984), and Lazarus and Folkman (1984). The Transactional Coping and Stress Model was formulated within an ecological systems theory perspective. One of the primary differences between the two models is that the model proposed by Wallander and Varni was developed to be a generic model, potentially applicable to a wide range of pediatric conditions (Wallander & Varni, 1998). To date, it has been used in studies investigating adaptation in children with a variety of different conditions (e.g., cerebral palsy, diabetes, sickle cell disease, spina bifida, and upper limb deficiencies) and, in some cases, adaptation of their mothers (Malik & Koot, 2009; Noojin & Wallander, 1997; Vermaes, Janssens, Mullaart, Vinck, & Gerris, 2008; Wallander et al., 1989; Wallander & Varni, 1998). In contrast, the Transactional Stress and Coping Model was developed primarily for children with sickle cell disease and cystic fibrosis and it continues to be used by investigators interested in understanding adaptation in families of children living with these two conditions (Barakat et al., 2007; Brown

et al., 1993, 2000; Gold et al., 2008; Thompson et al., 1993; Thompson & Gustafson, 1996; Thompson et al., 1994; Thompson et al., 1992). Lipinksi and colleagues (2006) used the Thompson model as a framework for interpreting the relationships between parents' perceived personal control and their reports of helpfulness of genetic counselors – a primary source of medical information for families facing the diagnosis of a genetic illness.

Both of these risk–resistance adaptation models consider a child's chronic illness to be a potential stressor to which the child endeavors to adapt. In addition, a major tenet of both models is that modifiable risk and resistance factors can be identified empirically. In the Wallander and Varni model, resistance factors (e.g., intrapersonal factors, stress-processing factors, and social-ecological factors) are conceptualized as potential protective factors because one's status in these areas might buffer the child from experiencing any potential negative consequences due to the child's chronic condition (Burlew, 2002). In the Thompson model the relationship between the child's chronic illness and adjustment varies as a function of parent (e.g., cognitive processes used to appraise stress and coping processes) and family processes (e.g., family functioning and family dynamics) (Burlew, 2002). Moreover, the relationship between the child's chronic illness and adjustment (i.e., maternal and child adjustment) varies as a function of biomedical, developmental, and psychosocial factors (Thompson & Gustafson, 1996).

Risk Factors

In the original model proposed by Wallander and Varni (1989), risk factors included (1) disease/disability parameters (e.g., diagnosis, handicap severity, medical complications, bowel/bladder control, visibility, cognitive functioning, and brain impairment), (2) functional dependence in the activities of daily living, and (3) psychosocial stressors (e.g., disability-related problems, major life events, and daily hassles). Eventually, functional dependence was changed to functional independence (e.g., hygiene, ambulation, and communication) (Wallander & Varni, 1998).

Risk factors included in the Transactional Stress and Coping Model are (1) illness parameters (e.g., type and severity) and (2) demographic parameters (e.g., child's gender, child age, socioeconomic status). In the expanded Transactional Stress and Coping Model developed by Gold et al. (2008), illness parameters are hospital visits; demographic parameters include sibling's gender, sibling's age, sibling's grade level; and socioeconomic status and family parameter were also added (e.g., extended family size).

Resistance Factors

Resistance factors in the Wallander and Varni (1989) are delineated into three categories: (1) interpersonal factors (e.g., competence, temperament, effectance motivation, and problem-solving ability), (2) social-ecological factors (e.g., family psychological environment, social

support, family members' adaptation and practical resources available to the family), and (3) stress-processing factors (e.g., cognitive appraisal and coping styles). In the Transactional Stress and Coping Model (Thompson & Gustafson, 1996; Thompson et al., 1994, 1992, 1993), resistance factors include both maternal and child adaptational processes. Cognitive adaptational processes for mothers are appraisal-stress (e.g., daily hassles and illness tasks), expectations (e.g., efficacy and health locus of control), methods of coping (e.g., palliative and adaptive), and family functioning (e.g., supportive, conflicted, and controlling). Child adaptational processes include expectations (e.g., self-esteem and health locus of control) and methods of coping. The expanded model developed by Gold et al. (2008) also includes sibling adaptational processes (e.g., sibling coping, sibling self-efficacy, and perceived social support).

Adjustment/Adaptation Outcomes

Adjustment/adaptation outcomes in the model developed by Wallander and Varni (1989) are mental health, social functioning and, and physical health. In the Thompson model, adjustment/adaptation outcomes include maternal adjustment and child adjustment. Gold et al. (2008) added sibling adjustment to the Thompson model.

RESILIENCY MODEL OF FAMILY STRESS, ADJUSTMENT, AND ADAPTATION

The Resiliency Model of Family Stress, Adjustment, and Adaptation (McCubbin & McCubbin, 1993; McCubbin, Thompson, & McCubbin, 1996d) is a widely used conceptual framework that continues to provide valuable insight into why some families adapt and become stronger in the face of stressful circumstances, while others remain vulnerable and some deteriorate. In a recent tribute to Marilyn McCubbin (Feetham, 2008), it was noted that her work on the Resiliency Model and associated family measures was instrumental in changing the conceptualization and conduct of research about families caring for a member with a chronic condition. The development of the Resiliency Model played a critical role in helping researchers and clinicians focus on resilience and adaptation in families living with chronic conditions (e.g., Brody & Simmons, 2007; Chen & Rankin, 2002; Leske, 2003; Mu, 2005; Robinson, 1997; Tak & McCubbin, 2002; Van Riper, 2000, 2007). Prior to the development of the Resiliency Model, researchers and clinicians typically focused their attention on family dysfunction and pathology (Feetham, 2008).

The Resiliency Model is an outgrowth of the evolution of family stress theory (McCubbin et al., 1996d). It builds on Hill's ABCX stress model (Hill, 1949) and later family stress models, such as The Double ABCX Model of Adjustment and Adaptation, the FAAR (Family Adjustment and Adaptation Response) Model, and the T-Double ABCX Model of Family Adjustment and Adaptation (Lavee, McCubbin, & Patterson, 1985;

McCubbin & McCubbin, 1989; McCubbin & Patterson, 1983; McCubbin et al., 1996d; Patterson, 1988). The Resiliency Model calls our attention to the ability of families to recover from adverse events. It is a strength-based approach – a model which highlights strengths and capabilities that influence the resiliency process.

The Resiliency Model is based on five basic assumptions about family life: (1) families face hardships and changes as a natural and predictable aspect of family life over the life cycle; (2) families develop basic competencies, patterns of functioning, and capabilities designed to foster the growth and development of family members and the family unit and to protect the family from major disruptions in the face of transitions and changes; (3) families develop basic and unique competencies, patterns of family functioning, and capabilities designed to protect the family from unexpected or nonnormative stressors and strains and to foster the family's recovery following a family crisis or major transition and change; (4) families draw from and contribute to the network of relationships and resources in the community, including its ethnicity and cultural heritage, particularly during times of family stress and crisis; and (5) families faced with crisis circumstances demanding changes in family functioning work to restore order, harmony, and balance even in the midst of change (McCubbin et al., 1996d, p. 14).

There are two phases in the Resiliency Model (McCubbin et al., 1996d): the adjustment phase and the adaptation phase. The adjustment phase depicts how families respond to events that do not present major hardships and only require minor changes in how the family is currently functioning or the initial response of the family to a more major event. The adaptation phase focuses on how families respond to major transitions or hardships that require fundamental structural or systematic changes in family functioning.

Because of the many challenges commonly associated with caring for a family member with a genetic condition, the adaptation phase is applicable to these families. Successful family adaptation (termed "bonadaptation") occurs when the family is able to achieve a balance between the needs of the family member(s) with the genetic condition, the needs of the family as a whole, and the needs of others in the family (McCubbin & McCubbin, 1993). Unsuccessful family adaptation (termed "maladaptation") occurs when the family is unable to achieve this balance.

According to the Resiliency Model, two families that appear to be undergoing similar experiences (e.g., raising a child with sickle cell disease) may respond differently, depending on a range of factors that shape the family process and outcomes of adaptation. These factors include *family demands or stressors*, *family types*, *family resources*, *family appraisal*, and *family problem-solving communication and coping*. Successful adaptation is more likely if families (a) have fewer other stressors or demands occurring at the same time (less pile-up of demands); (b) have family types or patterns of functioning that are more adaptive; (c) define the situation positively and view it as something they can master and have control over; and (d) have good coping and communication skills (McCubbin & McCubbin, 1993; McCubbin et al., 1996d).

Family Demands

Family demands include the demands on or in the family system created by (a) a family member having a chronic condition, (b) family life cycle changes, (c) prior unresolved family strains, (d) consequences of family efforts to cope, and (e) ambiguity at both the intrafamilial and the societal level (McCubbin, Patterson, & Wilson, 1996c). When an individual is diagnosed with a genetic condition, their family is most likely already dealing with many other demands. For example, in a family where the mother has just been diagnosed with hereditary breast and ovarian cancer, the family may already be dealing with escalating worry between the mother and the teenage daughter.

The genetic condition itself generally brings new demands and challenges to the family. Interactions with health-care professionals may be problematic and decisions about treatment choices can be agonizingly slow and difficult (Van Riper, 2001b). Uncertainty is common, especially surrounding the diagnosis of a genetic condition, treatment options, and the long-term prognosis (Mu, 2005; Van Riper & Selder, 1989). Moreover, for many genetic conditions, treatment options may be limited. Complex conditions may require the involvement of many health-care professionals and each of them may offer conflicting opinions about what the patient and family should do. Families who are already experiencing an accumulation or pile-up of demands will have more difficulty handling the demands associated with caring for a family member with a genetic condition than families who are experiencing fewer demands (Van Riper, 2000b, 2007).

Family Types

Family types are predictable and discernable patterns of family functioning (McCubbin et al., 1996d). While there may be many family types, three family types (i.e., *regenerative* family type, *resilient* family type, and *rhythmic* family type) have been associated with better physical and psychological health for family members and more adaptive functioning of the family as a unit. The regenerative family type is characterized by family hardiness (internal strength and a sense of control) and coherence (view of the situation as manageable and meaningful). These families are more likely to view the genetic condition as a challenge, something to be managed and mastered, and are committed to working together to solve problems as they arise. Closeness and flexibility are the key characteristics of the resilient family. Its members are able and willing to shift roles, rules, and boundaries as needed. That is, if a family member becomes ill or incapacitated due to their genetic condition, other family members are able to take over the ill member's roles and duties, family rules of operation can be altered, and the family is able to obtain outside help and information in order to manage the illness. For rhythmic families, time and routines are important. These families have established patterns and routines, such as having meals at a specific time each day, everyone eating dinner together, special bedtime rituals for the children, and specific strategies for keeping in touch with family members when they are away from home. In times

of illness and loss, the focus is on maintaining and valuing family time and routines because they provide stability and predictability. Of course, these typologies are not rigid or orthogonal in everyday life and families may share characteristics and express more or less of these typologies over time. This is critical to understanding how families adjust to genetic illness as the timing, severity, or course of disease onset among different members of the family may not be known in advance.

Family Resources

Family resources are the strengths and capabilities of individual family members, the family working as a unit, and the community (McCubbin, Comeau, & Harkins, 1996a). Families with adequate resources have a better chance of managing stress and restoring balance in their lives than families with limited resources (McCubbin & McCubbin, 1993). At the individual level, resources may include intelligence, physical health, stamina and endurance, a good sense of humor, an optimistic attitude, special knowledge and skills (e.g., problem-solving ability, computer skills), and psychological health (e.g., self-esteem, sense of mastery). Family resources that have been shown to play an important role in how families respond to stressful situations include cohesion, flexibility, open communication, routines, organization, shared spiritual beliefs, and economic stability. Community resources include the social, medical, friendship, and community-based networks and activities that the family unit can draw upon, access, and use to cope with crisis situations and bring their demands under control (McCubbin & McCubbin, 1993). Other community resources include services provided by churches, schools, libraries, and workplaces, such as access to health information, support groups, counseling, and access to communication technologies such as the Internet. Having access to Internet may be especially important to families with children with rare genetic conditions. For some families, it may be the only way for them to receive up-to-date information and support for their child.

Social support can be an individual-, family-, or community-level resource (e.g., support from extended family, friends, neighbors, coworkers, the church, the health-care team, support groups, and the workplace), and it is often viewed as one of the primary buffers or mediators between stress and psychological well-being (Tak & McCubbin, 2002). Findings from a study about family resiliency in childhood cancer revealed that parents who are supported in their workplace are better able to function within the context of their child's illness (McCubbin, Balling, Possin, Frierdich, & Bryne, 2002). Workplace support includes flexible schedules, opportunities to take time-off to be with a sick family member, and reassurance that the job will still be available once the parent returns to work. The willingness of coworkers to adjust their schedules to perform the tasks of the absent individual is a crucial part of workplace support (McCubbin et al., 2002).

Family Appraisal

In the adaptation phase of the Resiliency Model there are three levels of appraisal (McCubbin, Thompson, Thompson, & McCubbin, 1993b). The first level of appraisal is the family's appraisal of the stressor (e.g., the medical condition or diagnosis) and its severity. While one family may view their child's diagnosis of fragile X syndrome (an inherited genetic mutation on the X chromosome that affects the production of FMRP, a protein necessary for normal brain function) as a blessing because they finally have a diagnosis, another family may view it as a challenge that may lead to growth producing outcomes, and the third family may view it as a tragedy that will ultimately destroy the family.

The second level of appraisal is the family's situational appraisal (McCubbin, McCubbin, & Patterson, 1993a). A family's situational appraisal is the family's shared assessment of their demands, their capabilities, and the relationship between their demands and their capabilities. Or, more specifically, in the case of a family living with a genetic condition such as fragile X syndrome, the family's situational appraisal is an assessment of how well they are managing the ongoing demands associated with having a family member with fragile X syndrome given their individual, family, and community resources.

Family schemas are the third level of appraisal (McCubbin, Thompson, Thompson, & McCubbin, 1993b). Family schemas develop over time. They are a set of shared or accepted values, beliefs, rules, goals, priorities, and expectations that guide and shape major domains of family functioning, such as intergenerational responsibilities, disciplining and rearing children, and family–work relationships. Family schemas are more abstract than the other two levels of appraisal. They emphasize the overall meaning a family gives to the situation given its collective view of the world.

Family schemas are usually quite stable (McCubbin et al., 1993b), but they can be altered by the occurrence of catastrophic events such as the prenatal diagnosis of a lethal form of osteogenesis imperfecta (a genetic disorder characterized by bones that break very easily) or the unexpected death of a young father due to a heart attack caused by a mutation in a gene that affects the formation of blood clots. Families with a strong family schema are invested in the success of the family unit and they have a shared orientation that emphasizes the collective "we" rather than "I." They are guided by a relativistic view of life circumstances and a willingness to accept less than perfect solutions to their demands (McCubbin & McCubbin, 1989).

Family Problem-Solving Communication and Coping

Adaptation in families dealing with stressful situations, such as the diagnosis of a genetic condition, depends in part on the range and depth of the family's repertoire of problem-solving and coping strategies (McCubbin & McCubbin, 1993). Two types of family problem-solving communication have been found to predict family adaptation: incendiary communication and affirming communication (McCubbin, McCubbin, & Thompson,

1996e; Van Riper, 2000, 2007). Incendiary communication is characterized by verbal outbursts, a failure to calmly talk things through, and a tendency to bring up old, unresolved issues. In contrast to incendiary communication which tends to increase stress, affirming communication tends to decrease stress. When family members use affirming communication, they are careful not to hurt each other emotionally or physically, they take time to hear what other family members have to say, they convey respect for the feelings of other family members, and they end conflicts on a positive note. Families with an affirming style of problem-solving communication are better able to adapt to stressful situations than families with an incendiary style of communication (Leske & Jiricka, 1998; McCubbin et al., 1996e; Van Riper, 2000, 2007).

Family coping refers to "family strategies, patterns, and behaviors designed to maintain or strengthen the family as a whole, maintain the emotional stability and well-being of its members, obtain or use family and community resources to manage the situation, and initiate efforts to resolve family hardships created by a stressor" (McCubbin & McCubbin, 1993, p. 30). Families who use numerous coping strategies may adapt more successfully than families who use a limited number of strategies, especially if the strategies are passive strategies. In a study of parental and family adaptation in families raising a child with Down syndrome, the five most commonly reported coping strategies were (1) having faith in God, (2) knowing that we have the power to solve major problems, (3) facing problems "head on" and trying to get solutions right away, (4) sharing concerns with close friends, and (5) knowing that we have the strength within our family to solve our problems (Van Riper, 2007).

FAMILY MANAGEMENT STYLE FRAMEWORK

The development of the Family Management Style Framework (FMSF) involved 20 years of conceptual, empirical, and methodological work (Knafl, Breitmayer, Gallo, & Zoeller, 1996; Knafl & Deatrick, 1990, 2003; Knafl, Deatrick, & Gallo, 2008). According to a recent article by Knafl and colleagues (2008),

> The FMSF conceptualizes the interplay of how individual family members define key aspects of having a child with a chronic condition (Definition of the Situation), the behaviors they use to manage the condition (Management Behaviors), and their perceptions of the consequences of the condition for family life (Perceived Consequences). The resulting Family Management Style (FMS) is the pattern of family members' responses across these three components (p. 413).

The FMSF can be used to focus broadly on all aspects of living with a genetic condition or more narrowly on a circumscribed aspect of this experience, such as its bioethical dimensions. Under both conditions, the framework directs researchers and clinicians to focus both on how individual family members and the family unit as a whole actively manage

health-related challenges. In a recent tribute to the team of Kathy Knafl, Janet Deatrick, and Agatha Gallo (Bell, 2008), it was noted that the FMSF fills a unique niche in family research because it directs our attention to how families incorporate the management of a chronic condition into their everyday life. Thus, it helps set the stage for the development of assessments, interventions, and future research (Alderfer, 2006; Deatrick et al., 2006; Knafl & Deatrick, 2006; Nelson, Deatrick, Knafl, Alderfer, & Ogle, 2006; Thibodeaux & Deatrick, 2006).

The original FMSF was based on a systematic review of the literature that was undertaken to identify key aspects of how the family as a unit responded to chronic illness (Knafl & Deatrick, 1990). The three major components included in the original framework were *definition of the situation*, *management behaviors*, and *sociocultural context*. Definition of the situation was defined as the subjective meaning family members attributed to important elements of their situation (e.g., caring for a family member with a chronic illness). Management behaviors were considered to be efforts directed toward caring for the illness and adapting family life to the illness-related demands. The sociocultural context included culturally, ethnically, and religiously influenced values and beliefs as well as social, political, and economic structures and processes that shape how family members define and manage their situation. The initial description of the FMSF emphasized the interplay of family members' definitions of the situation and their management behaviors.

The original FMSF provided the conceptual underpinnings for a mixed-method study of 63 families in which there was a child with a chronic illness (Knafl, Breitmayer, Gallo, & Zoeller, 1994, 1996). In this study, conceptual dimensions or themes for the three major components of the framework were further refined and five distinct family management styles *(thriving*, *accommodating*, *enduring*, *struggling*, and *floundering)* were identified based on how two components of the FMSF (i.e., definition of the situation and management behaviors) were manifested within and across families (Knafl & Ayers, 1996; Knafl et al., 1996). This study provided support for using the FMSF to guide the identification of a broad spectrum of family management styles and for specifying unique areas of strengths and difficulties in families faced with the ongoing challenges associated with managing a child's chronic illness (Knafl & Deatrick, 2002).

In 2003, Knafl and Deatrick published an article describing a revised FMSF that includes further specification of its major components. The revised framework was developed following a review of results from 46 studies focusing on family response to childhood chronic conditions. Results of this integrative review supported the validity of two of the three components in the original FMSF (i.e., definition of the situation and management behaviors). They also provided support for including perceived consequences as a major component in the framework. As far as sociocultural context, the third component in the original FMSF, it was decided that it would be more appropriate to conceptualize sociocultural context as perceived influences on management rather than a major component of the FMSF itself (Knafl & Deatrick, 2003). The revised FMSF continues

to conceptualize family management styles as the configuration formed across all family members' definition of the situation and management behaviors.

As with the original FMSF, there are conceptual dimensions or themes for each of the three major components in its revision (Knafl & Deatrick, 2003; Knafl & Deatrick, 2006). For the definition of the situation component, the conceptual dimensions are *child identity* (parents view's of the child and the extent to which those views focus on normalcy and capabilities or vulnerabilities), *illness view* (parent's beliefs about the cause, seriousness, predictability, and course of the illness), *management mindset* (parent's views of the ease or difficulty of carrying out the treatment regimen and their ability to manage effectively), and *parental mutuality* (caregiver's beliefs about the extent to which they have shared or discrepant views of the child, the illness, their parenting philosophy, and their approach to illness). Conceptual dimensions for the management behaviors component are *parenting philosophy* (parent's goals, priorities, and values that guide the overall approach and specific strategies for illness management) and *management approach* (parent's assessment of the extent to which they have developed a routine orientation to illness management and their associated behaviors). As far as the perceived consequences component, the conceptual dimensions are *family focus* (parent's assessment of the balance between illness management and other aspects of family life) and *future expectations* (parent's assessment of the implications of the illness for their child's and family's future). While the eight conceptual dimensions are theoretically distinct, they are associated with each other to a certain degree.

The FMSF has been the guiding framework for at least two studies of families living with a genetic condition. The study by Gallo and colleagues (Gallo, Angst, & Knafl, 2009; Gallo, Knafl, & Angst, 2009; Gallo, Hadley, Angst, Knafl, & Smith, 2008) used a mixed-methods design to expand and refine the FMS framework to include family information management. In the study by Van Riper (Van Riper, 2004a, 2005; Van Riper & McKinnon, 2004), a mixed-methods design was used to expand and refine the FMSF to include family management of ethical issues that emerge during the genetic testing experience. Whereas Gallo and colleagues used a non-categorical approach, Van Riper used a categorical approach. The sample for the study by Gallo and colleagues included 86 families of children with various genetic conditions resulting from single gene mutations, including conditions such as phenylketonuria, sickle cell disease, cystic fibrosis, neurofibromatosis, hemophilia, thalassemia, Marfan disease, and Von Willebrand disease. The sample for Van Riper's study included 85 families in which at least one family member had undergone genetic testing for one of five genetic conditions (i.e., Down syndrome, sickle cell disease, cystic fibrosis, hereditary breast and ovarian cancer, factor V Leiden, and Huntington disease).

Findings from a qualitative analysis of data from the study by Gallo and colleagues (2001) revealed that the information sharing approaches and strategies used by parents in these families were grounded in the goal of promoting the child's adaptation to the genetic condition (Gallo, Angst,

Knafl, Hadley, & Smith, 2005). According to Gallo et al. (2005), parents shared information based on their assessment of the child's developmental readiness and interest. Typically, the sharing process unfolded over time. More recently, Gallo and colleagues (2009) identified four distinct information management types that reflect how parents access, interpret, and convey genetic information: (1) accurate understanding – open, (2) accurate understanding – selective, (3) discrepant understanding, and (4) confused understanding.

Cluster analysis was used to identify patterns of family functioning in a subgroup of the families in Gallo's study – those with two spouses (Knafl, Knafl, Gallo, & Angst, 2007). These patterns were based on both parents' assessments of family satisfaction and hardiness, as measured, respectively, by the Family APGAR and Family Hardiness Index. Cluster membership distinguished between parental reports of their own quality of life and their child's functional status. The clusters were non-categorical. That is, they did not depend on the child's specific genetic condition.

Until recently, one of the challenges faced by investigators using the FMSF was that unlike the Resiliency Model which has a number of behavioral assessment measures (e.g., Family Inventory of Life Events, Family Inventory of Resources for Management, Family Problem-Solving Communication Index) designed specifically to assess key concepts in the model (McCubbin et al., 1996d), there was not a measure designed specifically to assess key concepts or dimensions in the FMSF. However, such a measure now exists. The Family Management Measure (FaMM) was developed to describe how families manage caring for a child with a chronic condition/illness and the extent to which they incorporate condition management into everyday family life (Knafl & Deatrick, 2006; Knafl et al., 2009). The FaMM has 6 scales (53 items): family life difficulty (14 items), condition management ability (12 items), view of condition impact (10 items), condition management effort (4 items), child's daily life (5 items), and parental mutuality (8 items) (Knafl & Deatrick, 2006). The parental mutuality scale is not used with non-partnered parents.

The psychometric properties of the FaMM were assessed with a sample of 579 parents from 417 families of children with a wide array of chronic conditions (Knafl et al., 2009). Internal consistency reliability ranged from 0.72 to 0.91 and test–retest reliability from 0.71 to 0.94. Construct validity was supported by significant correlations in the hypothesized directions between FaMM and established measures (i.e., the Eyberg Child Behavior Inventory, Functional Status Measure, Global Functioning Scale of the McMaster Family Assessment Device). According to Knafl and colleagues, "results support FaMM's reliability and validity, indicating it performs in a theoretically meaningful way and taps distinct aspects of family response to childhood chronic conditions" (p. 1).

Definition of the Situation

According to Knafl and Deatrick (1990), a family member's definition of the situation is the subjective meaning they attribute to important

elements of their particular situation (e.g., being tested for a genetic condition, raising a child with a genetic condition). It includes the process of active construction of a definition of the situation and the content of that definition. Definitions of the situation change over time and they are based on multiple factors including cultural beliefs, familial rules and boundaries, and past experience with health-care providers.

An expectant mother's definition of the prenatal screening experience will most likely be based on a variety of factors including whether or not she has any other children, past experiences with prenatal screening for Down syndrome, and culturally based beliefs about being tested for and raising a child with Down syndrome. In addition, it will be influenced by any past experiences she has had with individuals with Down syndrome and her partner's views about prenatal screening.

An expectant mother's definition of the prenatal screening experience may change overtime. For example, in Van Riper's study (2004b) about the family experience of genetic testing, one mother's story vividly illustrates this point. Initially, Ann (a pseudonym), defined prenatal screening as a routine part of prenatal care – something that did not require much thought, something she had done with her other pregnancies. Later she defined it as a very stressful experience. Learning that her results suggested an increased risk of Down syndrome came as a surprise to her because she thought "Only women over age 35 have children with Down Syndrome." Unlike many of the health-care providers she encountered, Ann did not view the birth of a child with Down syndrome as a tragedy. She viewed it as a change of plans. It was something that she and her husband were willing to accept. It was her belief that "You keep your child no matter what." Ann reported, "It really didn't matter how he came out. If he did have Down syndrome or if he didn't." Ann sees her son with Down syndrome as more alike than different from typically developing children. According to Ann, "He looks different but he's got the same feelings and everything that we do."

Management Behaviors

Management behaviors are defined as discrete behavioral accommodations that family members use to manage their situation on a daily basis (Knafl & Deatrick, 1990). Like definitions of the situation, management behaviors can change over time. For example, an expectant mother who chooses to undergo prenatal screening for Down syndrome during her first pregnancy may decide not to undergo prenatal screening during subsequent pregnancies. One reason for this may be that her first prenatal screening experience ended up being too stressful because her initial results were positive (indicating that she was at increased risk for having a child with Down syndrome) and she had to wait 2 weeks to learn that the positive result was a false positive (the results indicated she had an increased risk for having a child with Down syndrome, but she actually did not). Moreover, a mother who gives birth to a child with Down syndrome despite being told that her results were negative (indicating that she was not at increased risk for giving birth to a baby with Down syndrome)

may decide not to have prenatal screening with her next pregnancy. Some mothers will make this decision because they feel they can no longer trust the test results. Or, it could be due to the fact that now that a mother knows what it is like to have a child with Down syndrome, she is not afraid to have an affected child.

Shortly after Ann was told that she was at increased risk for having a child with Down syndrome, she shared this information with her husband and they decided to continue the pregnancy without further testing. Her husband told her, "Leave it in God's hands. He [their child] is going to be who he is going to be no matter what." Ann found her husband and the rest of her family to be supportive and encouraging. Her husband never pressured her to terminate the pregnancy or give their child up for adoption. His response differed from the typical response of those in his country of origin. According to Ann, in her husband's native country "It's a disgrace to have a baby with Down syndrome or any kind of sickness. If a family has a baby with Down syndrome they take the baby to the church and drop it off." When Ann's health-care provider asked her if she wanted an amniocentesis, her response was "However he comes, he comes. I don't want to take the chance of miscarrying."

Perceived Consequences

Perceived consequences are the actual or expected individual, family, and illness outcomes that shape management behaviors and affect the subsequent definition of the situation. One of the consequences of Ann deciding not to have an amniocentesis was that each time she went to the clinic for an ultrasound (they were ordered weekly due to the detection of a cardiac defect) she was offered "The opportunity to terminate the pregnancy." This was very stressful to Ann. In fact, it was so upsetting to her that she considered not going to the clinic for the scheduled ultrasounds. Ann indicated that the failure of others to accept her decision to carry the pregnancy to term resulted in her feeling isolated. According to Ann, "They didn't move away, they stayed in their same place but they just moved away from me. It was like they just left me there."

Family Management Style

Family Management Style (FMS) is viewed as the configuration formed by individual family members' definition of their situation, the management behaviors individual family members engage in, and perceived consequences of the situation (Knafl & Deatrick, 1990, 2003; Knafl et al., 1996). The five family management styles (thriving, accommodating, enduring, struggling, and floundering) identified by Knafl and colleagues reflect a continuum of difficulties that families experience in managing a child's chronic condition and the extent to which the experiences of individual family members are similar or discrepant. For example, in a family with a thriving FMS, parents are likely to feel confident that they can manage both the usual and the unexpected challenges associated with their child's condition (Deatrick et al., 2006). Moreover, they are likely to

interpret the experience of parenting a child with a chronic condition in a similar way. In contrast, in a family with a struggling FMS, parental conflict is likely to be an overriding theme. This conflict is grounded in the parents' differing expectations of one another and their differing views of their situation.

Kendall and Shelton (2003) have identified the following four FMSs in families of children with attention-deficit/hyperactivity disorder (ADHD): chaotic, ADHD controlled, surviving, and reinvested. The chaotic family is characterized by extreme stress and disorder. They receive minimal outside support, maintain little if any interest in structure, and alternate between a general lack of responsiveness and the use of extremely rigid parenting strategies to deal with the behavior of the child with ADHD. In contrast, the reinvested family expresses a renewed sense of energy in managing the behavior of the child with ADHD. The parents use adaptive coping strategies that allow the family to feel restored and in control, rather than simply surviving. In a recent study by Conlon, Strassle, Vinh, and Trout (2008), all four of FMSs described by Kendell and Shelton were identified in a sample of families of children and adolescents with ADHD. According to Conlon and colleagues, identifying a family's FMS may improve our understanding of child–family interactions which, in turn, facilitates the development of effective interventions.

FAMILY SYSTEM GENETIC ILLNESS MODEL

The Family System Genetic Illness Model (FSGI) is a framework that can be used by family scholars and others to organize genomic conditions into clusters or groups in which the pattern of psychosocial demands associated with the conditions are similar over time (Rolland & Williams, 2006). The FSGI model is an expansion of the Family Systems Illness (FSI) Model (Rolland, 1984, 1987a, 1987b, 1990, 1994a, 1998, 2003), a model that is clearly grounded in systems theory. The FSI model is based on a strength-oriented framework; one that views family relationships as potential resources. Possibilities for growth are highlighted rather than just risk and liabilities. There is an emphasis on goodness of fit between family strengths and vulnerabilities and the psychosocial demands associated with the condition the family is dealing with over time. The following three dimensions are addressed in the FSI model: (1) psychosocial types of disability and illness, (2) major developmental phases in their natural history, and (3) key family systems variables (i.e., belief systems – culture/ethnicity, individual, family, and illness life cycles, and type of illness/disability/loss; Rolland, 1994).

Included in the FSGI model are a typology of genomic disorders and a schema of nonsymptomatic phases for genomic condition. Rolland and Williams (2006) recommend that these be used sequentially with the FSI model. The nonsymptomatic phases flow naturally into the three phases included in the FSI model (i.e., crisis, chronic, and terminal).

Psychosocial Typology of Genomic Disorders

The psychosocial typology of genomic disorders that was developed for the FSGI model groups genomic disorders according to the following characteristics: (1) likelihood of developing the condition (low, variable, high), (2) overall clinical severity of the condition (low or high), (3) time of clinical onset in the individual's life span (child/adolescent 0–20 years, early midadulthood child rearing 20–60 and later life >40 years), and (4) whether effective interventions exist to alter the clinical onset or progression of the condition (yes or no) (Rolland & Williams, 2006). There are 36 possible psychosocial types of genomic disorders. Each type has a distinct pattern of psychosocial demands based on it inherent biological and environmental responsive features.

Being able to group genomic conditions into these clusters is helpful to family scholars interested in comparative studies between families living with different types of genetic conditions. In addition, the ability to group genomic conditions according to their pattern of psychosocial demands helps determine if the findings from studies about families living with a certain genetic condition are applicable to families living with a different genetic condition. For example, sickle cell disease and Tay–Sachs disease are both autosomal recessive conditions (the gene mutation is located on one of the autosomes – chromosomes 1–22 and two copies of the gene are necessary to have the trait – one from the mother and one from the father). However, findings from a study about families living with Tay–Sachs disease (a fatal genetic lipid storage disorder in which harmful quantities of a fatty substance called *ganglioside GM2* build up in tissues and nerve cells in the brain) may not be that applicable to families living with sickle cell disease because the psychosocial demands associated with these two conditions are likely to be different. Using the typology developed by Rolland and Williams (2005, 2006), it appears that findings from a study about families living with cystic fibrosis might be a better choice because sickle cell disease and cystic fibrosis are the same psychosocial type of condition.

Sickle cell disease and cystic fibrosis are both autosomal recessive conditions in which (1) likelihood of the child developing the condition is high if the child has inherited the gene mutation associated with the condition from both their mother and their father, (2) the clinical severity is high, (3) the time of onset is usually during childhood, and (4) there are currently interventions to alter the clinical onset or progression of the condition. Tay–Sachs disease is also an autosomal recessive genetic condition in which the likelihood of a child developing Tay–Sachs disease is high if the child has inherited the gene mutation associated with the condition from both their mother and their father. In addition, it is also a condition in which the clinical severity is high and the onset of symptoms is during childhood. However, unlike sickle cell disease and cystic fibrosis, there are few, if any, interventions that can alter the clinical onset or progression of Tay–Sachs. Even with excellent care, most children with Tay–Sachs disease die by age 4, from recurring infection.

Nonsymptomatic Time Phases of Genomic Disorders

Due to recent advances in genetics and genomics, a growing number of individuals and families are learning they are at increased risk for a genetic condition. Moreover, this often occurs long before the clinical onset of symptoms. Therefore, it is useful to expand the time phases of illness included in the FSI model (i.e., crisis, chronic, and terminal) to include time phases that occur prior to the onset of symptoms. Rolland and Williams (2005) have identified four nonsymptomatic time phases: (1) awareness, (2) crisis I pretesting, (3) crisis II/posttesting, and (4) long-term adaptation.

In the awareness phases, there is some awareness of possible genetic risk, but there is no active consideration of testing or testing is not available. The crisis phase I starts when there is active consideration of testing. During this phase, there is some understanding of relevant genetic information and an awareness of possible psychosocial ramifications for individual family members and the family as a system. The crisis phase II includes the testing experience and the early posttest period. The long-term adaptation phase begins following awareness of the test results and it ends with the clinical onset of symptoms. There are critical transition periods between the phases. For example, during the transition between the crisis I phase and the crisis II phase, family members need to consider the fit of their life structure, plans, and dreams in the face of the developmental challenges ahead of them. Unfinished business in one phase can delay or block psychological movement to the next phase. Strategies that are adaptive in one phase may be maladaptive in another phase. For example, during the crisis I and crisis II phases, it may be very beneficial for family members to pull together. However, during the long-term adaptation phase, over-attentiveness may end up contributing to a family crisis.

Rolland and Williams (2005, 2006) have identified key individual and family developmental tasks associated with each of the nonsymptomatic phases. Key tasks for the phases are listed below (Rolland & Williams, 2006, p. 62):

Awareness Phase

1. Establish initial communication in family regarding illness and genetics.
2. Seek basic information regarding genetics of specific illness from primary care provider.
3. Consider whether individual family members could pursue genetic testing.
4. Cope and adapt to concerns about conditions where no genetic testing yet exists.

Crisis Phase I

1. Consider how decision might impact different nuclear and extended family members.
2. Gain understanding of genetics of illness.

3. Gain psychosocial understanding of illness.
4. Gain appreciation of developmental perspective.
5. View challenge of genetic knowledge as a shared one in "we" terms.
6. Consider who in family may be at risk and whom to inform.
7. Consider whom to include in decision making about whether to test.
8. Explore beliefs and meaning of genetics.
9. Make decision about testing: yes, no, defer

Crisis Phase II

1. Crisis coping and adaptation.
2. Accept permanence of genetic testing knowledge.
3. Maximize preservation of family identity before genetic knowledge.
4. Create meaning that promotes personal and family mastery.
5. Acknowledge possibilities of loss related to genetic risk while sustaining hope.
6. Develop flexibility in the face of uncertainty.
7. Consider implications of testing results for family members who test normal and at-risk members who have not been tested.
8. Establish functional collaborative relationships with health-care providers.
9. Adapt to any preventive treatments and health-care settings.

Long-Term Adaptation Phase (if test results are positive)

1. Maximize autonomy and connectedness for all family members within scope of genetic knowledge.
2. Minimize relationship skews.
3. Mindfulness of possible impact on current and future phases of family and individual life cycles.
4. Live with anticipatory loss and uncertainty.
5. Balance open communication (vs. avoidance, denial) and proactive planning with need to live a "normal" life, keeping threatened illness in perspective.
6. Maintain up-to-date genetic and medically relevant information.

Using the FSGI and FSI models together facilitates family scholars' and clinicians' anticipation of the psychosocial demands facing individuals and families living with a genetic condition. It also facilitates the development of more precise conceptualizations of the different types of genetic conditions. These conceptualizations can then be used to design and implement interventions for individuals and families living with genetic conditions that take into account the psychosocial demands of the condition, the illness or nonsymptomatic time phase, and the life cycle stage of both the individual and the family. These conceptualizations can be used to determine the timing and duration of interventions. Unlike other models

reviewed in this chapter, the empirical research base supporting the utility of the FSGI model has not been thoroughly evaluated. This represents an emerging opportunity for social and behavioral scientists to contribute concepts that support or refute central tenets.

RELATIONSHIP BETWEEN GUIDING FRAMEWORK AND PLAN OF CARE

As noted previously, observations of family functioning can differ based on conceptual orientation. This section includes a discussion of how the plan of care for Jennifer (the young woman with sickle cell disease from the case study) might vary depending on which framework is used.

Risk–resistance models are likely to focus most of their attention on Jennifer and her mother. In addition to assessing Jennifer's physical symptoms, they will assess risk and resistance factors that may be influencing how Jennifer and her mother are adapting to the current pain episode. Some of the risk factors they might assess include disease/disability parameters (e.g., type and severity of her sickle cell disease, other medical complications, cognitive functioning), functional independence (e.g., communication and ambulation), and psychosocial stressors (e.g., stressors related to living with sickle cell disease, daily hassles, and major life events). In terms of resistance factors they will most likely assess interpersonal factors (e.g., temperament and problem-solving ability), social-emotional factors (e.g., family psychological environment, social support, family members' adaptation, and available resources), and stress-processing factors (e.g., cognitive appraisal and coping styles).

If the Resiliency Model of Stress, Adjustment, and Adaptation is the guiding framework, the focus will expand beyond Jennifer and her mother to include other family members, especially other family members who have accompanied Jennifer to the emergency department. In the process of assessing family demands and family resources, one is likely to assess many of the same factors assessed under a risk–resistance model as a guiding framework. However, the Resiliency Model required a more in-depth assessment of how individual family members and the family unit as a whole appraise the situation. This may include appraisal at three different levels: (1) appraisal of the current pain crisis and its severity, (2) appraisal of how well the family is managing the ongoing demands associated with having two family members with sickle cell disease given their individual, family, and community resources, and (3) family schema – shared values, beliefs, rules, goals, priorities, and expectations that guide and shape major domains of family functioning, such as intergenerational responsibilities, disciplining and rearing children, and family–work relationships. For families like Jennifer's, the inclusion of an assessment of family schema is likely to be especially beneficial because it will make it clear that if different treatment options are presented, affected individuals will ultimately decide which option to take while parents and siblings may facilitate decision making.

The Resiliency Model is also more likely to assess problem-solving communication and coping at both the individual and the family level. This in turn will shed light on the fact that affected siblings may have different ways of communicating about and dealing with illness symptoms.

Moving on to the Family Management Style Framework (FMSF), this framework would likely require less in-depth assessment of risk and resistance factors. The assessment of how the family appraises or defines the situation will be similar to that done under the Resiliency Model, as will the assessment of problem-solving communication and coping. However, using the FMSF focuses greater attention on the family's overall management style and the extent to which the experiences of individual family members are similar or discrepant.

In Jennifer's family, an assessment of family management style would most likely suggest that the family be categorized as thriving, a family in which family members feel confident that they can manage both the usual and the unexpected challenges associated with sickle cell disease. This is important information because it suggests Jennifer and her family need and want to be included in decisions about her plan of care. Moreover, unlike some families who would rather have their family member stay in the emergency department or be admitted to the hospital if they need further care or monitoring, Jennifer's family would be comfortable providing the additional care and monitoring at home.

Finally, using a combination of the Family System Genetic Illness Model and the Family Systems Illness Model will give special attention to assessing the psychosocial demands commonly associated with sickle cell disease, the illness phase that Jennifer is currently in (i.e., chronic), and the life stage for Jennifer and her family. In this family, all of the family members have moved beyond nonsymptomatic.

CONCLUSION

Being tested for and living with a genetic condition is both an individual and a family experience. There is no single best lens or guiding framework to use when working with individuals and families affected by genetic conditions – an integrated framework, one that takes into account the perspectives of individual family members and the family as a whole, is productive. Relatively few of the researchers and clinicians who have written about the experience of being tested for and living with a genetic condition have reported using an integrated framework (see the following references for further critique of existing literature on this topic: Feetham, 1999; McDaniel & Campbell, 1999; Sorenson & Botkin, 2003; Van Riper, 2005, 2006; Van Riper & Gallo, 2005). Many have also not acknowledged the lens or framework used to guide their work. Those who do typically identify an individual framework. The scholarship of professionals who have applied an individual framework has generally run parallel to, rather than convergent with, those using family frameworks (Feetham & Thomson, 2006). This is a complementary approach and represents an additional opportunity to better integrate and expand the knowledge base

of individuals functioning in a family illness context and the functioning of families affected by genetic disease.

The five guiding frameworks presented in this chapter are overarching models that serve as starting points in understanding family experience. Yet, they do not capture the full richness and texture of families – no model can. The frameworks presented in this chapter are by no means the only frameworks that might help guide work with families being tested for and living with a genetic condition. Other frameworks that are well-worth considering are the Cumulative Stressor Model (Jaffee, Caspi, Moffitt, Polo-Tomas, & Taylor, 2007), the Posttraumatic Stress Framework (Kazak & Baxt, 2007), and the Illness Beliefs Model (Wright & Bell, 2009; Wright, Watson, & Bell, 1996) which is based on the Calgary Family Assessment Model and the Calgary Family Intervention Model (Wright & Leahy, 2005). Social and behavioral scientists are well poised to continue to make significant strides in translating and integrating genomics in medicine via a focus on children's and familial adaptation, needs, and resources. Solid grounding in such concepts and understanding interactions among domains may ultimately prove crucial to realizing the public health potential of genetic and genomic advance.

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6

Potential Impact of Genomic Information on Childhood Sibling Relationships

JOANNA FANOS, LORI WIENER, and TARA BRENNAN

INTRODUCTION

With the tremendous growth and excitement in the field of genomics, there is reason to be hopeful that evidence-based data on the experience of siblings will follow. As the field prospers, sibling relationships will be challenged by major issues, including differential interest in seeking carrier, pre-symptomatic and susceptibility testing, the handling of differential genomic data between sibling dyads, and the resultant apprehension and mastery. The potential impact of genomic information on childhood sibling relationships is largely not documented. Until the time that we have research on these issues, we turn to the literature on the impact of genetic information and illness on siblings and present existing data, largely based on conditions arising from single gene disorders.

Siblings of children with genetic disorders face daunting challenges. They encounter the prospect of genetic implications for their own lives and that of their children and confront the complexities of dynamics that evolve in families with a chronically or seriously ill child. As parental attention is focused on the affected child, well siblings are often neglected and their

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emotional needs ignored (Foster et al., 2001; Houtzager, Grootenhuis, Caron, & Last, 2005). In specialty clinics in which the affected children are seen, referral to professional psychological support is made rarely, typically only in crisis situations. Many institutions place pride in having embraced family-centered care, but these programs concentrate on empowering parents while continuing to neglect the compelling needs of siblings (Fanos, Fahrner, Jelveh, King, & Tejeda, 2005). Rarely has support for the well sibling been considered a priority, despite the growing body of literature that indicates that siblings of children affected by critical illnesses and genetic disease are at increased risk for psychosocial difficulties (Fanos, 1999a; Strohm, 2001; Taylor, Fuggle, & Charman, 2001).

This chapter will explore the impact of pediatric genetic illness on siblings. We will review the literature on family communication, sibling relationships, trauma and attachment theory, parental mourning, sibling guilt, and shame. In addition to existing literature, we will primarily focus on two serious pediatric genetic disorders, one autosomal recessive (ataxia-telangiectasia) and the other X linked (X-linked severe combined immune deficiency). This will include a comparison of the similarities and differences in sibling understanding of genetic information and perception of carrier status, as well as a comparison of the psychosocial impact on sibling relationships. As research on siblings of children with genetic disorders is relatively sparse, other diseases will be explored as well. Most notably, siblings of children with cancer appear to share the same psychological background and some of the same psychological consequences of the disease (Cuttini, Da Fre, Haupt, Giovanni, & Tamaro, 2003; Zebrack et al., 2002; Zeltzer et al., 1996). Therefore, this chapter will also include the experience of siblings of children undergoing cancer treatment, particularly those who become bone marrow and stem cell sibling donors. Clinical case examples will be provided to illustrate the similarities and differences between disorders, how these affect family functioning, and the sibling relationship. A summary of major issues and future directions will conclude the chapter.

RESEARCH BACKGROUND AND SCOPE OF THE PROBLEM

While some literature suggests potential positive effects of growing up with an ill sibling (Martinson & Campos, 1991; Packman, 1999; Williams, 1997), more frequently, researchers have reported a negative impact on emotional and behavioral functioning (Balk, 1990; Faux, 1993; Hutson & Alter, 2007; Pho, Zinberg, Hopkins-Boomer, Wallenstein, & McGovern, 2004; Sharpe & Rossiter, 2002). Psychosocial issues for well siblings include resentment, anger, anxiety, depression, jealousy, and guilt; fear of death; and emotional distance from parents (Fanos, 1996; Fanos, Davis, & Puck, 2001; Fanos & Wiener, 1994; Houtzager, Grootenhuis, & Last, 2001). Poor academic achievement, conduct problems, and difficulties in social relationships have been identified in healthy siblings of

children treated for cancer (Hamama, Ronen, & Feigin, 2000; Hefferman & Zanelli, 1997).

Unique psychosocial consequences exist in families where one child is affected by a life-threatening genetic illness. Siblings in families with rare genetic conditions may fear social stigma and peer rejection and thus be reluctant to talk to friends about the disease (Hutson & Alter, 2007). Siblings of children affected with genetic conditions may also demonstrate confusion and worry about the differences between being a carrier and being affected and the implication for future offspring (Hutson & Alter, 2007). Studies of adolescent and adult siblings of individuals affected with an inherited disorder, including X-linked severe combined immunodeficiency, cystic fibrosis, and ataxia-telangiectasia, indicate anxiety and depression, low self-esteem and self-concept, poor communication within the family, embarrassment, and guilt that they are not ill (Fanos & Gatti, 1999; Fanos & Johnson, 1995b; Fanos & Puck, 2001). Furthermore, several members of a family may be afflicted with an inherited disorder, and if that disorder is potentially or ultimately fatal, then well siblings may face the trauma of not one loss, but many (Fanos & Wiener, 1994). Long-term negative outcomes in adult siblings of individuals with cystic fibrosis report ongoing difficulties with survival guilt, anxiety, fear of intimacy, excessive worry about others, heightened feelings of vulnerability, sleeping difficulties, and somatic complaints, including headaches, ulcers, or symptoms similar to those of cystic fibrosis (Fanos, 1996; Fanos & Nickerson, 1991).

Studies drawn from the greater body of literature suggest that poor coping and maladjustment in siblings of ill children may be attributed, in part, to parents' effort to protect the sibling by providing a lack of information about the child's illness and encouraging minimal involvement in treatment (Fife, Norton, & Groom, 1987; Havermans & Eiser, 1994). On the other hand, positive adjustment has been associated with higher levels of family cohesion and adaptability (Cohen, Friedrich, Jaworski, Copeland, & Pendergrass, 1994; Horwitz & Kazak, 1990), lower levels of family disruption (Sloper & While, 1996), and enhanced intrafamiliar communication (DiGallo, 2003; Murray, 2002).

It is common for families with a chronically ill child not to communicate about the condition within or beyond the family (Fanos & Johnson, 1995b; Fanos, 1999a, 1999b; Fanos & Puck, 2001; Hardy, Armstrong, Routh, Albrecht, & Davis, 1994). Studies of siblings of children with cancer indicate that they cope better when informed about the condition and treatment (Kramer, 1984). Siblings who are not informed often feel excluded and express considerable anger at parents. Good communication prior to the death of a child continues on following the death, and both are correlated with better sibling adjustment (Birenbaum, Robinson, Phillips, Stewart, & McCown, 1989). Open communication between parents and siblings has been related to fewer behavioral problems and increased feelings of competence following the loss (Birenbaum, 1989). Keeping a family secret is a heavy burden for a sibling. Family secrets can lay the groundwork for traumatic responses (Van der Kolk, 1987), which may hinder a sibling's ability to grieve (Eth & Pynoos, 1985). Eth and Pynoos (1985)

emphasized that traumatized individuals must resolve traumatic elements of the loss before they are able to mourn. Many traumatized individuals find it difficult to handle their anxious and aggressive feelings (Van der Kolk, 1987). The symptoms of posttraumatic disorder – amnesia, detachment, obsessive thoughts, reliving the trauma – can occur in sibling loss (Fanos, 1996).

There is little information on how parents communicate the news of life-threatening illness to their children, particularly the healthy siblings. Families with a fatally ill child often struggle with determining whether the physician or the parent should tell the children. Recently, pediatric medicine has recognized the importance of developing a partnership between the health-care team, the child, and the family and emphasizes the importance of information exchange among these groups. New models for communicating with children and families emphasize the integration of medical and non-medical aspects of the illness (Weidner, 2007).

Attachment theory has explored the importance of emotional availability of the parent for the child's development. Researchers have found the difference between securely and insecurely attached children to be related to the caregiver's abilities to respond appropriately to the communications of the child (Ainsworth, Blehar, Waters, & Wall, 1978). Pound (1982) found depressed mothers to be impaired in their role, with difficulty being involved with their children's lives and showing them affection. The presence of a depressed or withdrawn mother can result in various developmental problems for the well sibling, including separation difficulties and disturbance in forming a normally assertive self (Levine, 1982). In normal development, through identifying with the strengths of the parent, the child perceives himself as competent. This sense of confidence may be disrupted when parents have been perceived as inadequate (Wahl, 1976). Self-psychology has described the lack of ability to identify with an adequate self-object as problematic for development of a child's self-esteem (Kohut, 1977). Siblings growing up in a family with a seriously ill child and depressed and anxious parents would be at risk for vulnerability in their sense of self (Fanos, 1996).

Research suggests that parents mourning the loss of a child grieve longer than was formerly assumed and experience long-term anxiety and depression (Kreicbergs, Valdimarsdottir, Onelov, Henter, & Steineck, 2004; Wortman & Silver, 1989). Frequent maladaptive responses of bereaved parents include idealizing or memorializing the deceased child, refocusing attention on the surviving sibling(s), or unflattering comparisons of the well sibling to the deceased child, all resulting in devastating consequences for the sibling's self-concept (Fanos, 1996; Fanos & Mackintosh, 1999; Fanos & Puck, 2001; Gibbons, 1992). Parental preoccupation with their own grief can have significant consequences: depressed parents may be impaired in their parenting roles; they may withdraw from other family members or prohibit them from talking about the child if it is too upsetting (Giovanola, 2005). Parental inability to help their children mourn can lead to intense fear and guilt in the survivor sibling (Cain, Fast, & Erickson, 1964). Parental accessibility, open communication, and support of the surviving sibling are vital to healthy adjustment (Rosen, 1985).

A COMPARISON OF DISORDERS: AUTOSOMAL AND X LINKED

To provide a more in-depth view of the above psychosocial issues of siblings of children with serious genetic pediatric conditions, we present two examples: work on autosomal recessive ataxia-telangiectasia (AT) and work on X-linked severe combined immune deficiency (XSCID). These disorders were chosen to illustrate some of the important differences between disorders in which both parents share equally in genetic culpability, and in which only one parent bears the entire genetic transmission burden. They will be compared to another autosomal recessive condition, cystic fibrosis (CF), the most common lethal disorder of Caucasians. Treatment for CF is extensive, primarily consisting of airway clearance techniques that enlist the help of family members. The impact on siblings has been described extensively in the literature, including books (Fanos, 1996; Summerhayes Cariou, 2006). Therefore, we will not be describing in depth the sibling impact, as we will with the lesser known disorders (AT and XSCID), about which far less has been documented in the literature. Similarities and differences among the three disorders will be explored, and the importance of acknowledging the specific characteristics of genetic conditions in terms of their unique impact on siblings will be discussed.

Siblings of Children with AT

AT is characterized by progressive cerebellar ataxia and oculocutaneous telangiectasiases, immune deficiencies, and increased predisposition to lymphoreticular malignancies (Brown et al., 1997). The gene for AT has been identified by positional cloning (Gatti et al., 1988; Lange et al., 1995; Savitsky et al., 1995). Siblings of AT-affected individuals who are heterozygotic for the AT gene may be at higher risk for cancer (Athma, Rappaport, & Swift, 1996; Easton, 1994; Morrell, Chase, & Swift, 1990; Swift, Reitnauer, Morrell, & Chase, 1987; Vorechovsky et al., 1996) and thus have their own health concerns, unlike carriers for the gene for CF or XSID.

Children with AT appear normal at birth; first signs typically appear in early childhood with delayed development of motor skills, lack of balance, and speech impediments. Due to progressively worsening ataxia (poor coordination and lack of muscle control), most children with AT are eventually confined to a wheelchair by age 10. Other hallmarks of this disease are the small dilated red “spider” veins (telangiectasia) which appear in the corners of the eyes or on the surface of the ears and cheeks. Approximately 70% of children with AT also have immunodeficiency that usually brings recurring and potentially life-threatening respiratory infections. Individuals with AT typically die in their teens or early twenties due to respiratory failure or cancer. Since no cure currently is available, treatment is primarily directed at alleviating symptoms.

Study of Siblings of Children with AT

In a qualitative study of parents and siblings of children with AT (Fanos, 1999a, 1999b; Fanos & Gatti, 1999), 35 siblings from 24 families, including 26 adults and 9 adolescents, were drawn from multiple clinical sites and interviewed for approximately 1 h. Semi-structured interviews were audio recorded and transcribed verbatim. Rating scales were developed on various categories capturing important aspects of family functioning and psychosocial adaptation; inter-rater reliability was obtained. The results illustrate major themes common to disorders with an autosomal genetic transmission pattern and ones with visible difficulties as well as considerable caregiving burden on siblings.

Understanding of Genetic Information and Perception of Carrier Status

Misconceptions about the genetic transmission of AT were common. Less than half of adult siblings responded within an acceptable range of prevalence for AT in the general population (between 500 and 1,000 diagnosed cases). Nearly twice as many of those whose responses were outside the acceptable range overestimated the prevalence (Fanos & Gatti, 1999). This distortion, perhaps due to the saliency of their experience, was similar to responses of siblings with CF (Fanos & Johnson, 1995b). Explanations given in childhood had been difficult for some siblings to understand. Personal carrier risks were underestimated by 84% of adult siblings, particularly noteworthy since these siblings had been exposed to technological advances such as DNA analysis, and therefore are likely more knowledgeable than the majority of families with a child with AT (Fanos, 1999b).

Myths surrounding their carrier status were common. Thirty-five percent of siblings believed they were carriers before giving blood, 11% thought they were not, and 54% had no preexisting beliefs (Fanos & Gatti, 1999). These data may be compared to siblings of individuals with CF, in which 53% of siblings decided they were carriers prior to testing, 15% believed they were not, and 32% had no preexisting beliefs (Fanos & Johnson, 1995b). Believing one is a carrier prior to testing has been reported as a way of sharing somewhat in the experience and thus binding guilt in CF (Fanos & Johnson, 1995a).

Assumptions of carrier status and of the self were transmitted from parental misconceptions. For some families, one parent interpreted the genetic reality as their spouse's fault. If blame was placed on the father, AT was seen as retribution for prior behavioral transgression. On the other hand, if blame was placed on the mother, her guilt was failing to achieve her biological task to produce a healthy child. Although individuals may have received written information on the genetics of AT, their deeply held beliefs about self and others influenced the way they viewed factual information (Fanos & Gatti, 1999).

Family Communication

Most siblings (79%) reported that communication in their family about the illness had been open. While siblings recalled conversations about the illness and the possibility of an early death, genetics rarely was discussed. Since physical limitations could not be hidden, there remained only one secret to keep – the genetic nature of the disease. The functional limitations due to AT frustrated well siblings, interfering with their ability to play and thus to bond with the affected child. Verbal communication was also problematic since the AT-affected child had a compromised ability to speak clearly. As healthy siblings entered adolescence and experienced widening of their interpersonal networks, the relationship became ever more distant. Interference with the attachment relationship was precipitated by various factors, including the affected child's locomotor and speech difficulties; withdrawal of the well sibling to avoid the pain of witnessing progressive debilitation; and the sibling's feelings of resentment, embarrassment, shame, and guilt.

Approximately one-fifth of participants expressed high resentment of the AT-affected sibling. Some siblings reported they had been forced to relinquish a social life to stay home to care for the sick child; thus their own developmental needs were sacrificed. Respondents experienced a role reversal in caring for, and developmentally surpassing, older ill siblings. For some individuals, this role confusion caused disturbances in identity formation (Fanos, 1999a).

Sibling Guilt

One half of the sample was rated as having moderate guilt. Some well siblings felt guilty about having felt resentful toward the affected sibling. A frequent dynamic was that well siblings wished to distance themselves from their brother or sister, felt shame, and then guilt about their feelings. When the well sibling was able to master a developmental stage that the affected child had been unable to reach, they felt guilt and sadness. Some siblings feared their ill sibling resented their ability to enjoy a healthy life. Another common theme was separation guilt from parents, similar to siblings of CF-affected individuals (Fanos, 1996). Those siblings who were able to leave home at an appropriate developmental time felt guilty for their feelings of relief and escape.

Most siblings of AT-affected individuals commented they were "sad" their brother or sister had AT but were relieved that they did not. This differs from siblings of CF-affected individuals, for whom survivor guilt was a major concern, leading to wishes to be a carrier (Fanos, 1996). Sibling identification with the AT-affected child was rare in this sample, probably due to the weakened bond between the dyad. Idealization of the ill child was not an issue for participants in this study, as we shall see in our sample of siblings of XSCID-affected individuals as well (Fanos, 1999a).

Case Example – Sibling of Individuals with AT

Susan was a young woman in her mid-twenties that grew up with two brothers with AT. She always believed that she was a carrier, primarily because of frequent bouts with respiratory illnesses, similar to the symptoms she had witnessed in her brothers. Communication in the family was open; she reported that she knew what she needed to know at appropriate times. Her mother had made it clear to her from a young age that her brothers would eventually become very ill and die.

There were many times when she felt that it was unfair that she could not just be a child free from worries. She reported feeling that she had to take on the role of being both a sister and a mother to them. When she was only 16 years of age, her mother took her out of school in order to help care for her brothers. She feels that she will never forgive her mother for not allowing her to remain in school and to graduate with her classmates. Since being taken out of school, she suffered from serious depression and had frequent dreams of having to protect her brothers from some threat outside of the home. In addition, she had a recurring dream for over 10 years. In the dream, she was running through a field and someone was chasing her to kill her. She knew she had to do something, so she would find a large rock and beat them to death with it. She believes that the dream may have represented her relationship with her mother.

Susan always thought she would never bear children in order to avoid the chance of having affected offspring. Recently, she learned that the gene had been identified and that testing was possible; thus, she is reconsidering her choice. She fears that if she does not bear children, she will be "missing something." On the other hand, Susan feels that she has already given so much of herself to caretaking responsibilities in her early years that focusing on her own needs would be most important to her at this time.

Siblings of Children with XSCID

SCID is a serious immune disorder; over half of SCID in humans is X linked (XSCID). XSCID is caused by mutations in the gene IL2RG, which encodes a receptor for interleukin-2 and multiple other cytokines (Buckley et al., 1997; Noguchi et al., 1993; Puck et al., 1993; Sugamura et al., 1996). While SCID was inevitably fatal in infancy, the introduction of bone marrow transplantation (BMT) improved the prognosis considerably (Gatti, Meuwissen, Allen, Hong, & Good, 1968). Although early diagnosis and BMT currently enable survival for over 80% of males with XSCID, this treatment has usually required hospitalization lasting several months. Delayed or inadequate antibody production requires monthly immunoglobulin replacement for periods from 2 years to indefinitely, so parents continue to worry about exposure to germs. XSCID is widely known as the "bubble boy" disease, referring to David Vetter, a boy with XSCID, who lived for years in a plastic, germ-free bubble.

Study of Siblings of Children with XSCID

A study was conducted on parents and siblings of boys with XSCID (Fanos et al., 2001; Fanos & Puck, 2001), stemming from the referral of affected probands and their healthy female relatives for genetic testing since 1987. In that year, a family workshop was organized at the National Institutes of Health, bringing together a cross section of enrollees in ongoing protocols, including 132 individuals of XSCID-affected families. For the study cited below, all families who had attended the workshop and could be located were invited to participate.

Forty adult siblings of individuals with XSCID were interviewed from 14 families (37 females, 3 males). One-fourth of siblings were born after the death of their affected brother(s). Of those siblings who were alive when an affected brother died, the mean age of the participant at death of their brother was 7 years. Participants were interviewed, interviews were transcribed verbatim, coding scales developed, and inter-rater reliability obtained.

Understanding of Genetic Information and Perception of Carrier Status

Sixty-two percent of adult siblings had no preexisting beliefs about their carrier status, 23% believed they were not carriers, and 15% believed they were (Fanos et al., 2001). These data are in contrast to adult siblings of individuals with AT, in which 35% believed they were a carrier, and CF, in which 53% thought they were (Fanos & Johnson, 1995b). Several factors may be responsible for the lesser tendency to develop personal myths in XSCID, including slightly higher odds of being a carrier in AT and CF, and the fact that some of these individuals had attended a workshop. Sixteen percent of siblings felt flawed by being a carrier of this mutation. Many siblings felt their carrier status lessened their desirability (Fanos & Puck, 2001).

Severe anxiety about adult sibling's unaffected child's health was not an issue in this sample (Fanos et al., 2001), similar to results from the AT study (Fanos & Gatti, 1999). This finding differed from some other serious pediatric genetic conditions such as CF, in which anxiety was more prevalent (Fanos & Johnson, 1995b). There are two possible reasons for the lower anxiety in siblings of XSCID-affected individuals. First, in XSCID, even though daughters may be carriers, they will not have the disease. Second, parents knew their affected baby was sick during his first months of life, unlike disorders such as CF in which the symptoms can develop later. In XSCID, parents are reassured once the health status of the newborn is established.

The characteristics of XSCID, including its mode of inheritance, severe infantile presentation, and current availability of effective treatment, shaped the attitudes of these families; their level of knowledge was superior to those of families struggling with conditions with progressive, relentless deterioration (Fanos et al., 2001).

Family Communication

The majority of siblings of males affected by XSCID felt that communication in their family had been poor, creating an atmosphere laden with family secrets. Parents tried to protect well siblings from disturbing information, and well siblings sheltered parents from the distress of answering questions. Those siblings who were alive during their brother's illness found it difficult to understand what was happening. Some siblings whose brother had passed away before they were born learned that they had had a brother by accidentally finding an object such as a photo hidden in a drawer. Others did not learn about their brother until their own adolescence, when older siblings divulged the secret and asked them not to tell anyone, including their parents (Fanos & Puck, 2001).

Sibling Relationships

Sibling resentment was not a major problem in XSCID families (Fanos & Puck, 2001). This differs from chronic disorders such as CF, in which the family focuses on the ill child for years, creating sibling resentment (Fanos & Johnson, 1995b; Fanos, 1996). In XSCID, the child either died soon after birth or had a transplant and thus a relatively normal childhood. The need for isolation and fears of contamination had weakened the attachment between the affected and the well siblings; thus, identification with and idealization of the affected sibling were not an issue in XSCID. This is similar to AT (Fanos, 1999a). However, many daughters perceived that their parents preferred male offspring. Thus male gender was idealized, with profound implications for self-esteem for sisters.

Many siblings voiced concerns about separation from their mother during the hospitalization of their affected brother. Often, mothers spent long periods at the hospital with the sick child, away from the rest of the family. Fathers were left trying to balance working long hours away from home while attempting to care for the well children.

Sibling Guilt

Guilt was not a major issue for this sample, since there was little resentment over which to feel guilty. The guilt that was expressed focused on four areas. First, siblings worried that they may have brought germs into the home, particularly if their brother had died. Second, siblings with their own affected offspring felt guilt about being a carrier. Third, mothers who were carriers felt guilty about passing on the carrier burden to daughters. Finally, siblings with no affected males felt guilty watching their sisters endure distressing medical procedures with their children (Fanos & Puck, 2001). In this sample, few sisters expressed wishes to be a carrier, unlike siblings of individuals with CF, who used this wish as a way of binding guilt (Fanos & Johnson, 1995a). In addition, sisters of males with XSCID expressed no belief of deserving retribution.

One-third of siblings chose careers in the health professions, primarily nursing. Several siblings recalled their mother returning from the hospital

and praising the nurses who were caring for their child (Fanos & Puck, 2001). The tendency of siblings of ill children to select a medical career has been reported previously in AT in which more than a third of the adult sample had chosen a career in the medical professions (Fanos, 1999b).

Parental Mourning

The majority of siblings believed their mother had never successfully mourned the loss of her son. Those families in which the sibling reported poor family communication were those in which siblings felt their parents had been unable to mourn (Fanos & Puck, 2001). Daughters in families with unresolved mourning felt an intense desire to have a healthy son. This represented both an attempt to repair the mother's unresolved loss and a wish to repair the injury to the sense of self of being a carrier. This finding had not been encountered in previous studies of CF and AT, both autosomal disorders in which the genetic guilt was shared by both parents.

Case Example – Sibling of Males with XSCID

Beth was in her mid-forties at the time of the interview; she is married and is a nurse. Prior to the availability of BMT, she lost three brothers when she was 7, 12, and 13 years, respectively. Following the first death of a brother when she was 7 years of age, she recalled returning home and starting to cry and having her mother angrily ask what she was crying about. She believes that her mother feels very guilty about being a carrier and that it is exclusively her fault. Many memories of her mother involve her coming home from her brothers' hospitalizations and talking about how kind and important the nurses were to her and how deeply they had touched her. Beth believes that she became a nurse because of her mother's deep respect and love for the nurses.

Beth always knew that her drive to reproduce was extremely strong. Since she held the belief that being a carrier implies one is flawed and defective, she wished to feel normal. She did not know if she wanted a child as much as she wanted to be a member in the "mother club." She also felt that her reasons for wanting a child involved winning a battle and cheating death, so that she could have a boy that would not die. In addition, she believes she wanted to have a son to give to her mother as a replacement for the ones that she had lost. Beth still has a sense of being outside the circle of life.

Comparisons Between CF, AT, and XSCID: Key Similarities and Differences

Many psychological issues for siblings of children are similar in families with a child affected by CF, AT, and XSCID. In all three, well siblings confront the possibility of death of their brother or sister, overwhelmed parents who are depressed and anxious, and serious genetic realities with implications for their own lives. Many families struggling with genetic

disease attempt to conceal as much as possible. Families with CF tried to hide the possibility of early death of the affected (Fanos & Johnson, 1995b; Fanos, 1996); families with AT, a highly visible disorder, hid the genetic component (Fanos, 1999a). Families with XSCID concealed the prior existence of affected boys (Fanos & Puck, 2001).

In families in which the illness itself can be concealed (e.g., CF), the possibility of early death for the affected sibling was often handled as a family secret (Fanos, 1996). Consequently, the child's death was experienced by the sibling as a trauma, resulting in posttraumatic stress disorder (Eth & Pynoos, 1985; Horowitz, 1997; Terr, 1991; van der Kolk, 1987). In CF, watching the ill sibling receive more attention fueled resentment, envy, guilt, idealization of the sibling, and expectation of retribution by being a carrier.

In families with a child with AT, the condition could not be hidden; therefore, it was obvious to the sibling that the affected child needed more attention (Fanos, 1999a). While there was resentment over the burden of caregiving, and interference with identity development, there was little or no envy and less need to idealize the sibling as a defense against guilt over envious feelings (Klein, 1957). However, in AT, the visibility of the disorder disrupted the ability of the family to present itself to others as normal, with efforts exerted to manage the stigma. The embarrassment that this may elicit, and the resulting shame and guilt, is destructive to the sibling dyad and the sibling's developing sense of self. Thus in AT, the dynamic is one of burden rather than trauma. In addition, siblings felt shame over their embarrassment. The expressed reactions of rage at others for calling attention inappropriately to the sibling's disability provided evidence of the magnitude of the disavowed shame and self-hatred.

In XSCID, the family secret/trauma was that there had been a brother who was born and died (Fanos & Puck, 2001). If parents did not provide an explanation for their needing to spend more time with the sick child, the well sibling may feel less loved. In XCID, siblings' perceived abandonment by the mother while she kept watch over the ill child during the BMT hospitalization injured self-esteem. In addition, the X-linked nature of the disorder caused a sense of self as flawed, differing from autosomal recessive disorders in which the genetic responsibility is shared. The desire to have a healthy son on the part of daughters in XSCID is both an attempt to repair the injured sense of self as a carrier and a desire to repair the mother's loss of her own son.

The specific phenotype predisposes the dynamics in the family that will impact the sibling. Conditions vary in terms of visibility, potential for early death, caregiver burden, and so forth. Medical professionals must take into account differences of genetic disorders they encounter in order to offer appropriate psychosocial support to siblings.

SIBLINGS AS BONE MARROW AND STEM CELL DONORS

Many of the issues that have been presented so far permeate throughout the sibling childhood cancer experience. Childhood cancer can be very disruptive to family life and emotional well-being (Houtzager et al., 2004).

It is common for young children whose brother or sister has cancer to be frightened that the disease is contagious and that they too will develop cancer. They may be worried about their sick brother or sister but feel resentful about the attention their sibling with cancer is receiving, guilty for having these emotions and for being healthy, and angry about the lack of physical and emotional availability of parents. When a sibling dies, survivor guilt is a commonly expressed emotion. Siblings who seem to adapt well are those whose parents, extended family, and community provide support; there is an absence of parental depression; the family is cohesive; there is a lack of secrecy; and effective parent–sibling communication about the illness exists (Cohen et al., 1994). In the case of the sibling donor, understanding genetic information is critical whether the transplant is to treat a primary genetic disorder or a malignancy.

Stem cell transplant (SCT) or BMT has evolved over the past two decades from a heroic, experimental therapy of last resort to a first-line therapy for many life-threatening hematologic and oncologic diseases (Lipton, 2003). In addition to malignant and non-malignant disorders and hematologic disorders (sickle-cell disease and thalassemia), allogeneic stem cell transplants may be an appropriate intervention for children with genetic disorders, such as immunodeficiency syndromes, osteopetrosis, and metabolic storage disorders. Among pediatric patients undergoing SCT, 75% receive healthy stem cells from a brother or sister (Packman, Gong, VanZutphen, Shaffer, & Crittenden, 2004). With approximately 2,000 SCT transplants performed annually in the United States with patients less than 20 years old (Center for International Blood and Marrow Transplant Research, 2005), a critical need exists to understand the psychosocial impact of donation in order to guide clinical care (Wiener, Steffen-Smith, Fry, & Wayne, 2007).

The majority of studies examining the psychological functioning in sibling donors are limited to BMT donors. While higher distress in pediatric donor than non-donor siblings has been noted, most studies have been limited by small sample sizes, non-representative samples taken from single institutions, and qualitative and cross-sectional designs (Wiener et al., 2007). Reported psychological reactions to the experience have included depression, withdrawal, behavioral problems, lowered self-esteem, identity problems, psychopathology, guilt, resentment, post-trauma symptoms (Packman et al., 1997, 2004), and anger following the donation procedure (MacLeod, Whitsett, Mash, & Pelletier, 2003; Packman et al., 1997; Wiley, Lindamood, & Pfefferbaum-Levine, 1984). Risk factors for poor psychological functioning include age at donation with a risk of unresolved developmental crises in adolescence (Packman et al., 1997), recipient death (MacLeod et al., 2003), transplant complications such as graft versus host disease (GVHD) or graft failure (MacLeod et al., 2003), limited involvement in donation decisions (MacLeod et al., 2003; Packman et al., 1997), feeling coerced to donate (Packman et al., 1997), limited preparation for transplant complications (MacLeod et al., 2003; Packman et al., 1997), and individual sibling characteristics such as preexisting psychopathology (Packman et al., 2004). In XSCID, resentment of having had to be a donor, threats to the sense of self upon not being chosen to be the donor, and damage to self-esteem upon death of the recipient

led to potential long-term negative consequences for siblings, both donors and non-donors (Fanos & Puck, 2001). A positive response to the donor experience, such as improved family relationships, along with heightened intimacy between recipient and donor, has also been described in conventional BMT donors (MacLeod et al., 2003; Wiley et al., 1984).

As sibling donors are actively involved in the transplant process, their experience of the patient's illness varies from that of healthy non-donor siblings, though the risk for problematic adjustment and behavioral issues may still be present (Stuber, 1996). Anecdotal and descriptive reports address the intense stress that siblings experience as a result of the recipient's illness, the procedure to collect their own stem cells including possible physical harm to themselves, separation from family during the period of post-transplant hematopoietic recovery, and possible post-transplant complications, including the subsequent death of the patient (MacLeod et al., 2003; Wiener et al., 2008). Whether or not the transplant is successful, each sibling's family life will be interrupted by the transplant experience. Transitioning beyond the transplant, siblings will have "good days and bad days" and this experience frequently parallels the transplant trajectory (Wilkins & Woodgate, 2007) and his or her pre-illness personality. Therefore, obtaining a comprehensive psychosocial assessment of the sibling donor's strengths and vulnerabilities prior to transplant and having a solid understanding of how the sibling might cope if the SCT is unsuccessful (including whether the parents might unconsciously blame the donor child) are essential components to the donation process.

The need for such psychosocial assessment and support prior to genetic testing is compelling for families where one child has already been diagnosed with a serious illness. This is often the case when a transplant is under consideration. In such situations, the patient and his or her siblings will be tested to determine their tissue type or human leukocyte antigen (HLA) type. HLA types are determined by molecular typing in which the DNA of the recipient and prospective donor are characterized to identify specific genes that direct the formation of the HLA antigens on the surface of cells. Similar to waiting for genomic information to be disclosed, significant anxiety is often manifested while waiting to find out if a match is available. The following vignette illustrates this distress as well as the importance of family communication, sibling relationships, and guilt.

Case Example

Samuel was diagnosed with acute lymphoblastic leukemia at 11 years of age and was treated with standard chemotherapy. He was in remission for 2 years before relapse. At this point, an allogeneic SCT was recommended and the family began the process of HLA typing. Sam lives with his biological parents and younger sister. Sam's sister Dawn presented with anxiety manifested by difficulty sleeping, clinginess, and frequent crying spells a week prior to her appointment for HLA testing. This was followed by the development of a facial tick, complaints of stomach and chest pains, and eventual school refusal. A psychological exam elicited persistent worrying focused on fears associated with losing her brother,

finding out she was a match and having to undergo a medical procedure to collect her stem cells, and/or learning she has or will develop cancer. Dawn expressed profound guilt associated with the possibility of being a match and her brother subsequently rejecting her stem cells, getting sicker, and dying. She also expressed frustration that her brother is often "mean to her" and that their relationship has been "awful since he got sick." She wondered if he would do the same for her if she were diagnosed with a life-threatening disease.

Counseling with Sam's sister and family was initiated prior to testing and focused on education surrounding the testing, the impact of her brother's diagnosis on the family, reduction of guilt, sadness about the changes in their relationship and the lack of closeness she was feeling, and learning new ways to communicate effectively within the family. Counseling continued during and after the waiting period, and this provided Dawn and her family with additional, much-needed psychological support. Some important issues to consider prior to testing include the psychological benefit to the child, competing interests between the child and the parents/family, whether the child can give informed assent/consent, and whether the timing to undergo testing is right in order to make a psychological assessment and prepare the child and family for testing (Chittenden, 2009).

Preparation: Assessment and Interventions

With no published data-driven clinical guidelines, psychosocial and medical practices pertaining to donor preparation and assessment vary from center to center and are largely based on anecdotal evidence, provider preference, and clinical experience (Phipps, 2009). However, due to the known stresses of donation, donor assessment prior to, during, and following transplantation is recommended, depending on the age of the donor. Investigations should include multiple measures of psychosocial adjustment as well as qualitative designs that allow investigators to learn from the donors themselves how they are coping with the SCT experience. A separate interview with the prospective donor is recommended beginning at approximately the first grade age level. In addition to conversations and assent documents, written material should be provided to donors and their parents. Depending on the donor's age and learning style, this could include booklets, coloring books, and videos, in addition to one-on-one conversations with members of the transplant team and other sibling donors about the SCT.

Pre-implantation Genetic Diagnosis

When SCT is the treatment of choice, compatible donors may not be available. In such cases, parents might consider in vitro fertilization (IVF) and pre-implantation genetic diagnosis (PGD). PGD allows parents with a child suffering from a life-threatening disease to select an embryo that will be a perfect tissue match with an older sibling. The baby's stem cells are then transplanted to the affected sibling with the hopes of curing the

disease. The introduction of technically sophisticated treatments such as PGD into the clinical setting may have a powerful potential to prevent illness and cure disease in novel ways, but determining whether the embryo (and potential child) would be a suitable tissue donor for a seriously ill sibling, when there is no actual benefit for that potential child, introduces clinical, ethical, and social dilemmas (Brown & Webster, 2004).

In fact, since its emergence, PGD has sparked controversy and been opposed by many groups. While evidence shows that PGD is safe with children born following IVF and has no higher rate of birth defects than children of normal pregnancies, ethical issues concern conscientious objection to direct participation, discarding of healthy but unsuitable embryos, and valuing "savior" or "designer" siblings in themselves, not just as means to the other sibling's ends (Bennett, 2005; Dickens, 2005). When PGD is being considered, it is essential that physicians and counselors assess the parent's motivations to assure that the donor child is not at significant risk of harm and exploitation. Some questions to review with parents include the following: Will the child be expected to provide whole organs to the older child later in life if that is necessary? What psychological effect will this have on the child, the older sibling, the rest of the family? (Kahn & Mastroianni, 2004). Most parents will welcome suggestions on how best to explain the unique circumstances surrounding their birth when their children are old enough to understand.

Since siblings may be at risk themselves for a related disease, genetic testing is often considered for the well siblings in the family. Even with evidence of clear medical benefit, the psychosocial risks and benefits for the child and the family for these patients should be assessed, discussed, and weighed appropriately. If the issues have been thought through and the family and provider decide to go forward, then genetic testing has the potential to be a powerful tool in arming the family with knowledge to aid them in early detection and/or prevention of disease (Chittenden, 2009).

SUMMARY AND CONCLUSION

This chapter explored the impact of serious pediatric illness on siblings. We reviewed the literature on family communication, sibling relationships, parental mourning, and sibling guilt and shame; focused on several serious pediatric genetic disorders; and described their differential impact on siblings. The psychosocial effect of BMT and SCT on siblings has also been discussed.

Providing attention to the psychological health of the well sibling is critical. About 20–30% of children in the United States suffer from a chronic disease or health condition, many severe enough to impact daily life (US Census Bureau, 2005). The vast majority of these children have well brothers or sisters. Increasing recognition of the unique needs of siblings of children afflicted with serious conditions can be seen in the burgeoning body of support groups for siblings such as Sibshops (Meyer & Vadasy, 1994), summer camps such as Camp Okizu (Packman, Fine

et al., 2004), and children's books with such informative titles as *I Wish I Was Sick Too!* (Brandenberg, 1978) and *When Brothers and Sisters Get Sick* (Peterkin, 1992). Regional support programs such as the Sibling Center in San Francisco (Fanos et al., 2005), as well as national programs (SuperSibs.org), and web sites for sibling support (e.g., "Band-aides and Blackboards" and "The Sibling Connection") attest to the growing awareness of and response to the need.

Siblings of children with known genetic conditions face several challenges. Not only do they encounter the complexities of family dynamics that evolve in situations with a chronically or seriously ill child, they face the prospect of genetic implications for their own lives and that of their children. New genetic discoveries will have sobering implications for numerous childhood illnesses that currently are not specified as genetic. Newborn screening programs will identify an ever-increasing list of conditions about which little is known. Indeterminate and ambiguous results will cause parental distress and preoccupation that may interfere with the ability to parent both the affected child and the siblings. Since brothers and sisters in families in which a child is identified with a disorder through newborn screening may not be able to be tested until they are adults, sibling relationships may be affected in important ways. All of these recent developments need to be addressed in future research.

Medical professionals must recognize the seriousness of the impact of pediatric illness on the well sibling and develop effective models of providing support. Siblings will create various modes of growing from and mastering their experience, as many already have done, and achieve resolutions that will lead and inspire others. With unique and powerful voices, siblings will tell the story of their experiences in the years to come.

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7

Family Communication of Genomic Information

BRENDA J. WILSON and HOLLY ETCHEGARY

INTRODUCTION

Genetic information is inherently both personal and familial. While knowledge of personal genetic risk often generates information relevant to other family members (information flow from consultand to relatives), in many situations the first suspicion of genetic risk is itself prompted by shared information within a family, that is, the family history (information flow from relatives to consultand). Thus, except in contexts where genetic testing is offered to all members of a general target population (e.g., newborn screening), the discovery or clarification of genetic risk generally depends on the sharing of information between family members. In clinical genetics as practiced in Western culture, therefore, there is a paradoxical situation in which family information is often pivotal in risk assessment procedures, but an individual consultand, whose genetic status may have been clarified through the sharing of "family information," may also have the right to prevent disclosure of what is now "personal information" to other family members.

The conflicts inherent in this situation have promoted discussion of whether genetic information should be viewed as different from other types of health information and treated as belonging to the family (Annas, Glantz, & Roche, 1995; Gostin, 1995; Gostin & Hodge, 1999; Parker & Lucassen, 2004; Lucassen, 2007). While professional and regulatory bodies recognize the relevance of genetic information for family members beyond the consultand, most prioritize the protection of privacy over the duty to warn. Guidance may be absolute or near absolute: for example, the French National Consultative Ethics Committee for Health

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and Life Sciences clearly indicates that the trust in the professional–patient relationship must never be undermined by breaking confidentiality (National Consultative Ethics Committee for Health and Life Sciences, 2003) and the National Society of Genetic Counselors' Position Statement on Confidentiality of Test Results states that "It is the right and responsibility of the individual to determine who shall have access to his/her own medical information, including genetic information" (National Society of Genetic Counselors, 2002). Some professional bodies emphasize the importance of discussing the communication of genetic information as part of the pre-test counseling process and view this as the best way of fulfilling the provider's obligation to other family members (American Society of Clinical Oncology, 2003; Taub, Morin, Spillman, Sade, & Riddick, 2004). Finally, some bodies support the primary importance of preserving individual confidentiality while allowing for the possibility that disclosure to a relative against a consultand's wishes may be legitimate when the magnitude of potential harm from nondisclosure outweighs the harm of breaching confidentiality. In general, the following conditions are often set as a test for whether confidentiality may legitimately be breached (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1983; World Health Organization, 2003):

- Reasonable efforts have been made to persuade the individual to disclose the information voluntarily and have failed.
- There is a high probability that harm to the relatives (possibly including future children) will occur if the information is not disclosed and there is evidence that the information could actually be used to prevent harm.
- The harm averted would be serious. Some bodies suggest that the harm should also be "imminent" (American Society of Human Genetics, 1998).
- Precautions should be taken to ensure that only genetic information directly relevant to the identified relatives' own medical status would be revealed. Information relevant to the individual must remain confidential.

In reality, the burden of proof of probable, serious harm presents a high bar for many genetic conditions, thus shifting the focus on to communication of genetic risk as a primarily voluntary activity on the part of consultands. The limited evidence which exists does in fact indicate that most consultands want or intend to share information. A recent study of intention to disclose BRCA1/2 genetic test results reported very high levels of intention (up to 91%) to disclose to first-degree relatives (Barsevick et al., 2008). A prospective study in the United Kingdom and Australia calculated a rate of "clinically significant" non-disclosure of less than 1% (Clarke et al., 2005). Research consistently finds high frequencies of communication with first- and second-degree relatives and less communication with those relatives who are less closely related (Forrest, Delatycki, Skene, & Aitken, 2007; Forrest et al., 2003). While it seems that over 99% of consultands communicate genetic information to relatives (Clarke et al.,

2005), the scant research available on family members (as potential recipients) suggests that there is often only limited awareness that (1) a genetic condition was present in their family, (2) they themselves were at risk, and (3) genetic testing and a variety of preventive options were available (Sermijn et al., 2004). Thus, it seems that the majority of people having genetic tests appear willing to share genetic risk information with other family members, but they may not do so in a way that facilitates understanding of risk information in recipients (Peterson et al., 2003; Sermijn et al., 2004).

The main purpose of this chapter is to describe the current state of knowledge about how decisions are made to communicate or not, the processes of communication, and the impact of disclosure or nondisclosure of genomic information. From a clinical perspective, the key benefit of sharing genetic information between relatives usually revolves around the clarification of the risk status of other family members and the associated counseling and possible clinical interventions which ensue. In effect, this is a case-finding approach, in which the goal is to ensure that people who could benefit from risk assessment are identified and counseled. However, just as the existence of a genetic disorder within a family has implications, effects, and symbolism which go beyond strictly clinical concerns, so do issues around communication demand broader attention. Communication of risk information may depend on "active persuasion" by a genetics professional (Elwyn, Gray, & Clarke, 2000), which is an exception to the general principle of non-directiveness in counseling. Some bodies go so far as suggesting that genetics professionals have the obligation to "ask assertively" for help in contacting at-risk relatives (World Health Organization, 2003).

Another important issue is how to support consultands who wish to share genetic information with other family members, but face difficulties in doing so, for example, because of feelings of guilt, anticipated disbelief on the part of information recipients, or the perceived need to challenge strongly held family "myths" about disease or disease risk (Wilson et al., 2004). Sometimes the issue is quite simply that a consultand does not feel equipped to communicate complex medical information adequately.

Although interest in communication is not new, and has been reflected in more general studies of families and genetics (e.g., Pincus & Dare, 1978), specific research interest in this area has generally reflected the recent rapid expansion in genetic knowledge and the increasing availability of genetic tests. Two recent reviews (Wilson et al., 2004; Gaff et al., 2007) identified about seventy primary research studies concerned with family communication published since the early 1980s, of which around half had been published since 2004. In the policy arena, the issue has received explicit attention particularly since the inception of the Human Genome Project in 1990; in policy, regulatory and professional statements, it has been addressed most often as a clinical practice issue relating to professional protection of privacy and the duty to warn family members (American Society of Human Genetics, 1998; National Society of Genetic Counselors, 2002; American Society of Clinical Oncology, 2003; World Health Organization, 2003; Taub et al., 2004).

FAMILY COMMUNICATION AS PROCESS

Communication of genetic risk information among families is a complex process affected by numerous individual, family, and disease characteristics, as well as sociocultural factors (DeMarco & McKinnon, 2007; Wilson et al., 2004). As a result, a substantial number of both barriers to, and facilitators of, family communication of genetic information have been identified. In this chapter, we review the current literature relating to family communication and suggest that these barriers and facilitators are intricately related to both the process and the function of family communication.

The term "disclosure" is often used in relation to the communication of genetic information; while it is useful as a description of a situation at a given time (information having been "disclosed" or "not disclosed"), it promotes the idea of passing on information as a single, discrete event. This ignores the complexity of communication, which may be better viewed as "a verbal and non-verbal process whereby different signs, symbols, and silences are just as important as language and talking" (Forrest et al., 2003; Wilson et al., 2004, p. 318). Gaff and colleagues (2007) concluded that the communication of genetic risk information is best thought of as a deliberate process including a number of actions. These include making sense of personal risk (Forrest et al., 2003; Hamilton, Bowers, & Williams, 2005), considering the effects of disclosure, deciding upon exactly what information to disclose, and planning the timing of disclosure (Gaff et al., 2007; Hamilton et al., 2005).

Forrest and colleagues (2003) suggested that, before people disclosed genetic risk information to other family members, they needed time to make sense of their own risk before deciding whether and what to tell relatives. Further, those who perceived their risk as ambiguous or uncertain had more difficulties with disclosure. This first step in the process of disclosing risk information to other family members may function as a barrier to communication if consultands have difficulty comprehending the meaning of their own risk.

When people do decide to disclose genetic information, they consider the effects of disclosure on relatives, particularly children (Forrest et al., 2003; McAllister et al., 2007). There is a dilemma underlying disclosure decisions: the desire to provide family members with risk information that is perceived to have important health and social ramifications is weighed against the desire to protect relatives from emotional and psychological distress (d'Agincourt Canning, 2006; Hamilton et al., 2005). In general, family members' vulnerability to the information, as well as their receptivity to it, is assessed prior to disclosure, and these assessments are based mainly on relatives' life situation and personality (Hamilton et al., 2005). Vulnerability is assessed by considering the amount of upset or worry disclosure could cause, as well as the mental or physical health of the relative (Hamilton et al., 2005). For example, Sobel and Cowen (2000) reported that their participants had decided to whom they would disclose test results based on whether their relatives could "handle it." Receptivity can be assessed by considering whether relatives would want the

information (Hamilton et al., 2005). For example, if people perceived that relatives would not act upon the information or they had already experienced a relative's denial of the family illness, they were less likely to disclose risk information about inherited high cholesterol (IHC) (van den Nieuwenhoff, Mesters, Gielen, & de Vries, 2007).

Alternatively, receptivity can sometimes be assessed by considering (correctly or otherwise) whether the risk information is relevant to a particular family member at all (e.g., a perception that boys do not "need" to be told about risk for breast cancer; Forrest et al., 2003). Thus, the second step in the process of disclosure can contain any number of barriers to communication depending on the assessment of family members' vulnerability and receptivity.

Inherent in communication decisions is a consideration of exactly what information to disclose (Gaff et al., 2007). Individuals can be selective in what they disclose; for example, a study of families affected by Huntington disease (HD) found that individuals disclosed a range of information, from suspected symptoms, to their consideration of genetic counseling, to their test results (Klitzman, Thorne, Williamson, Chung, & Marder, 2007). Hamilton et al. (2005) reported that people at risk for hereditary breast–ovarian cancer (HBOC) disclosed more of the information gained during genetic testing than did people at risk for HD. For example, the former discussed the need for others to be tested, family duty to children, family members' reproductive choices, and treatment options. In contrast, those at risk for HD disclosed little more than test result, unless asked to by siblings.

A consideration of the timing of disclosure is also part of the process of family communication of genetic risk. There is a concern to disclose at the "right time," particularly when communicating with children (Forrest et al., 2003; Gregory et al., 2007; Klitzman et al., 2007). The right time could refer to key life transition phases (e.g., getting married, having children), but it could also simply be the time at which children were perceived to be old enough to understand. The teller also had to feel it was the "right time" in that he or she was emotionally ready to disclose (Hamilton et al., 2005). Practically, the right time could also refer to opportunities for family gatherings during normal social contact where disclosure could take place (Forrest et al., 2003), although it is also noted that the celebratory nature of some events might work against feeling able to communicate "bad news."

Research has also observed the importance of "zones of relevance" (Cox & McKellin, 1999; Parsons & Atkinson, 1992), that is, the conditions under which genetic risk becomes salient and its meaning for the individual and the family considered. Zones of relevance include critical life junctures such as meeting a life partner, planning to start a family, or beginning university or a new career. They also include episodes of illness within the family (Cox & McKellin, 1999; Petersen, 2006). It is perhaps not surprising that family communication of genetic risk is facilitated during these zones of relevance.

Models of family functioning highlight family communication as a key component influencing both family cohesion and flexibility (Olson, 2000).

Positive communication skills facilitate healthy levels of family cohesiveness and flexibility, whereas poor communication skills are thought to hinder a family's ability to change when needed (Olson, 2000). It is recognized that the progression from suspected risk of illness to the diagnosis of illness in an individual represents a period of great change and upheaval for a family (Rolland & Williams, 2005). As such, the development of effective interventions to assist families in communicating about genetic risk information seems a worthwhile goal. In order to do so, however, we need to know exactly what happens in families as they communicate about genetic risk.

COMMUNICATION BARRIERS AND FACILITATORS

Most research on family communication of genetic risk information focuses on late-onset disorders, including HD (Hamilton et al., 2005; Klitzman et al., 2007), HBOC (Hamilton et al., 2005; MacDonald et al., 2007), and hereditary non-polyposis colorectal cancer (HNPCC) (Aktan-Collan et al., 2007; Mesters, Ausems, Eichhorn, & Vasen, 2005; Pentz et al., 2005). Other conditions studied include balanced translocations (Suslak, Price, & Desposito, 1985; Wolff, Back, Arleth, & Rapp-Korner, 1989), recessive and sex-linked disorders such as cystic fibrosis (CF) (Wilson et al., 2004), inherited high cholesterol (van den Nieuwenhoff, Mesters, Nellissen, Stalenhoef, & de Vries, 2006; van den Nieuwenhoff et al., 2007), and hemophilia (Gregory et al., 2007). In general, the findings are consistent in their identification of barriers and facilitators which are outlined below. We follow the broad classification of barriers and facilitators used in Wilson and colleagues (2004) which include disease, individual, family, and sociocultural factors.

Disease Factors

Inheritance Pattern

Various forms of inheritance carry different disease risks for family members and may influence how and when people discover their own risk, as well as how or if they share risk information with relatives. In recessive disorders, for example, there may be too few cases in the family to recognize a clear pattern of inheritance (Richards, 1996), potentially limiting family communication about the disorder. In general, the evidence is conflicting in recessive and sex-linked disorders, as well as chromosome translocations, about whether genetic risk information is shared with relatives (Wilson et al., 2004). For example, some work on family communication in families affected by CF has documented difficulties in disclosing carrier information, finding only partial disclosure so that some relatives were not aware of their carrier risk (Denayer, De Boeck, Evers-Kiebooms, & van den Berghe, 1992; Ormond, Mills, Lester, & Ross, 2003). In contrast, the presence of a close affected family member may facilitate communication about CF risk in the family (Ormond et al., 2003).

More recent work reported that most parents shared their child's suspected or confirmed CF status with family members and also disclosed relatives' carrier risk (Dillard & Tluczak, 2005). In families affected by hemophilia, at-risk carrier women reported few difficulties with communication. In general, their disclosure practices followed gender lines for this X-linked disorder, sharing risk information mainly with mothers and sisters (Sorenson, Jennings-Grant, & Newman, 2003).

A recent study observed differential communication patterns in obligate and non-obligate carrier families affected by hemophilia (Gregory et al., 2007). In that study, nondisclosure to daughters occurred more often in families where the father was affected with hemophilia than in those families where a son was affected. The authors speculated that since fathers were less likely to have accidents or require treatment, the day-to-day lived reality of the condition was more "invisible" to daughters, hence there was less need to talk about the condition. This was contrasted with disclosure to daughters in families with an affected son. In this case, daughters were told about their brother's condition and the need for them to "take care" in social activities with their affected brothers (Gregory et al., 2007, pp. 191–192).

It cannot be assumed that autosomal dominant transmission, presumably a more identifiable pattern of inheritance, assures more open communication and awareness about genetic risk (Wilson et al., 2004). In some families affected by HD, for example, family risk becomes salient only when a close relative is diagnosed, sometimes out of the blue (Cox, 2003; Etchegary, 2006). The sudden, unexpected discovery of HD in a close family member, despite a limited awareness of HD in distant relatives, affects subsequent disclosure decisions (Klitzman et al., 2007).

The timing of discovery of one's own genetic risk has also influenced disclosure behavior in the context of HBOC (Forrest et al., 2003) and HNPCC (McAllister, 2002). Interviews with members of HNPCC families revealed several social factors that either facilitated or blocked the process of engaging with cancer risk (McAllister, 2002). For example, personal experience with a relative with cancer and family "talk" about cancer were identified as causal conditions that influenced engagement with cancer risk. Further, ignorance of the family history and lack of personal experience with an affected relative were identified as intervening conditions that blocked the process of engagement. Engagement may be an important concept in genetic risk communication since highly engaged individuals may be more likely to disclose risk information to other family members.

Important barriers to communication are lack of awareness of which family members might be at risk and misunderstandings about patterns of inheritance. For example, inherited high cholesterol (IHC) is a group of hereditary lipid disorders (e.g., familial hypercholesterolemia) that increases carriers' risk for premature cardiovascular disease. van den Nieuwenhoff et al. (2006) found that disclosure was less likely to occur if patients were unaware that particular relatives could be at risk. Misconceptions about the inheritance pattern of IHC, for example, believing IHC could skip a generation, also acted as a barrier to disclosure (van den Nieuwenhoff et al., 2007).

Disease Severity and Preventability

Research has not fully clarified the influence of disease severity and preventability or treatment options on the disclosure of genetic risk information. Some research suggests that more open styles of communication are reported in HBOC and HNPCC families than in HD families because of the difference in potential risk reduction strategies and treatment (Forrest et al., 2003; Peterson et al., 2003). The stigma sometimes associated with HD has also been suggested to foster a closed communication style in some HD families (Klitzman et al., 2007). Lehman and colleagues (2000) used hypothetical vignettes to explore participants' opinions on disclosure practices for preventable and non-preventable conditions. Participants were more likely to agree that patients should inform relatives when the disease was preventable than when nothing could be done to prevent the disorder. In contrast, a more recent vignette study found that disease severity and preventability did not influence agreement that genetic information should be shared with relatives. However, participants were generally more likely to agree that family members should be tested for preventable conditions (Crabb, Tucker, & Young Mun, 2005).

Certainty of Test Results

Complicating family communication, the growing technical ability of DNA sequencing enables the detection of increasing numbers of gene variations whose risk and clinical consequences are unknown (van Dijk et al., 2004; 2005). Accordingly, these sequence alterations have been designated variants of uncertain clinical significance (VUCS), and they are detected in a significant portion of test candidates.

It is also possible to receive an inconclusive test result; that is, a consultand with a strongly suggestive family history tests negative for a BRCA1/2 mutation in the absence of a known familial BRCA mutation (van Dijk et al., 2004, 2005). This means that another, currently unidentified, mutation ("BRCAx") might be related to the candidate's strong family history of cancer. Women receiving an inconclusive test result, therefore, may be left with considerable uncertainty and psychological stress about their genetic risk (Bish et al., 2002), making it difficult to understand their own risk or the meaning of their risk for relatives (DeMarco & McKinnon, 2007; Farkas Patenaude et al., 2006). The ambiguity of much genetic risk information may hinder disclosure to family members. For example, in HBOC and HNPCC families, members with uninformative test results were less likely to disclose risk information than those who received informative results (Farkas Patenaude et al., 2006; Wilson et al., 2004). Such findings highlight the need for research on the comprehension and communication of inconclusive test results. With the advent of predictive testing for additional multifactorial diseases (e.g., thrombophilia, cardiac disease, diabetes), uninformative test results will likely be more and more common, and more families may need professional guidance and support in communicating ambiguous test results.

Individual Factors

Emotions

A number of psychological factors affect the disclosure of genetic risk information in families. Emotional reactions to risk information, including feelings of guilt, shame, or blame, may hinder family communication of genetic risk, particularly in families affected by HD which is stigmatizing for some family members (Etchegary, 2007; Klitzman et al., 2007). Alternatively, feelings of guilt can motivate people at risk for inherited cancer and IHC to undergo testing with the express purpose of providing risk information to relatives for their own risk management behaviors (d'Agincourt-Canning, 2006; Hallowell et al., 2006; van den Nieuwenhoff et al., 2007). This perception of genetic responsibility can create an emotional burden for at-risk individuals. Indeed, communication of important information about hereditary cancer is often perceived as difficult, not the least of which is due to fears about causing anxiety in other family members (Hallowell et al., 2003). Hallowell and colleagues (2003) noted that disclosure of genetic risk information generates an ethical dilemma for at-risk individuals in that they perceive a responsibility to inform kin, but must then accept that they may cause harm and worry to family members.

Coping Strategies

People's coping strategies for their own risk will also affect family communication about the disorder, on the part of both the messenger and the receiver. Personality differences between those family members who want to know about their risk and those who do not could reflect a different style of coping with health risk information more generally (Miller, 1996). "Monitors" attend to and are more likely to process threatening information, while "blunters" avoid health threat information and cues. For example, blunters may be less likely than average to see a physician or seek information in the face of a health threat. Thus, it is plausible that monitors may be more likely to share genetic risk information, though we are unaware of any research that has specifically measured this outcome. Prior research does confirm, however, that monitors are more likely to participate in health screening studies and genetic testing (Tercyak, Bennett Johnson, Roberts, & Cruz, 2001a).

Other coping strategies in the form of psychological defense mechanisms such as denial and rationalization have been observed to hinder communication in both HD and HBOC families, as well as families affected by thalassemia (an inherited blood disorder) (Hallowell et al., 2006; Klitzman et al., 2007; Petersen, 2006). Similarly, risk denial and a fatalistic perspective about genetic risk acted as barriers to family communication about IHC (van den Nieuwenhoff et al., 2007).

Family Factors

Type of Relationship

Research suggests that the nature and distance (both social and geographic) of the relationship between family members influence family communication of genetic risk. Across a range of disorders, disclosure is more common to spouses and first-degree relatives and to those family members to whom people feel emotionally close. In contrast, disclosure of genetic risk information to distant relatives is less likely to occur or is carried out in a more selective manner (Klitzman et al., 2007; Kohut, Manno, Gallinger, & Esplen, 2007; Mesters et al., 2005; Petersen, 2006; van den Nieuwenhoff et al., 2007; Wilson et al., 2004).

The most frequently cited reasons for not informing distant relatives are lack of emotional closeness, not knowing the family member, or lack of routine contact (Wilson et al., 2004). For example, Petersen (2006) reported that geographical distance of family members acted as a barrier to family communication across a range of disorders, including CF, hemochromatosis, hemophilia, and thalassemia. People at risk for IHC also cited lack of contact, particularly with second- and third-degree relatives, as a reason for nondisclosure; specifically, "some participants indicated that it would feel strange to suddenly contact estranged relatives" (van den Nieuwenhoff et al., 2007, p. 1030). Emotional and/or geographic distance acted as barriers to communication in research with families affected by inherited cancers (Macdonald et al., 2007; Pentz et al., 2005) and HD (Klitzman et al., 2007). Emotional distance is not the only barrier to communication with distant relatives. For example, Klitzman et al. (2007) reported that among siblings at risk for HD, emotional distance was a barrier to communication about the family risk.

Family Communication Between Parents and Children

Relatively little research focused on the process of communication about genetic risk between parents and their children and the subsequent outcomes for children in living with this information (Metcalfe, Coad, Plumridge, Gill, & Farndon, 2008). This focus is important, however, since approximately 50% of mothers share BRCA1/2 test results with minor-age children within a month of receiving them (Tercyak et al., 2001b). Similarly, about 50% of BRCA1/2 mutation carriers disclosed test results to their older children (15–38 years), immediately after receiving them (Segal et al., 2004).

A growing body of work suggests that family communication between parents and children is a complex behavior with psychological and emotional consequences for both parent and child. Recent research suggests that disclosing BRCA1/2 genetic risk information to children consisted of three phases: the predisclosure phase, the disclosure phase, and the impact of disclosure phase (Clarke, Butler, & Esplen, 2008), each with its own challenges. Clarke et al. (2008) reported that women experienced decisional conflict around communication with offspring, particularly with

daughters: "... the decision to disclose was often described as an emotionally laden challenge, in attempting to balance the moral obligation to disclose whilst needing to protect the child from the impact of the genetic information" (p. 800). Other research confirms that the decision to disclose BRCA1/2 risk to children is associated with elevated levels of distress in mothers (Tercyak et al., 2001b).

These findings were confirmed in a recent meta-synthesis of studies about parent–child communication across a range of genetic disorders (Metcalfe et al., 2008). While parents often expressed a strong sense of responsibility to discuss information about inherited risk with their children, parents reported that, "... they, and their children, found discussion difficult and that openness did not lessen the psychological and emotional pain of living with the condition and knowledge of your own possible risk" (p. 1196). Very few studies have considered outcomes of communicating genetic risk to children; of those that did, mothers reported that children's overall behavior or well-being was not adversely affected (Metcalfe et al., 2008). In contrast, in those families with closed communication patterns, children were often frustrated with the family secrecy and relationships between family members were tense (Metcalfe et al., 2008).

Some BRCA1/2 carriers reported that their children expressed significant concern about their mother's future health, as well as their own testing options following disclosure (Segal et al., 2004). They also noted that older children tended to want more information and facts, approach the situation in a more logical manner, and show more concern for their mother's health. Younger children, on the other hand, expressed a higher level of worry, as well as a stronger interest in testing and prevention (Segal et al., 2004).

For the mothers, some experienced a feeling of "ongoing dishonesty" toward their children, as well as feelings of guilt at the possibility of having passed on the mutation to their offspring (Clarke et al., 2008). Despite these concerns, however, Metcalfe et al. (2008) concluded in their review that parents who openly communicated with their children did not regret doing so. Further, in families with open communication, children were reported to be more psychologically and emotionally resilient. It is notable that majorities of parents in studies included in the review reported a complete lack of support/advice from health-care professionals regarding the communication of genetic information to children (Metcalfe et al., 2008). However, several studies report parental interest in a variety of disclosure interventions. For example, Tercyak and colleagues (2007) found that mothers undergoing BRCA1/2 testing endorsed several information resource needs including literature about options and what to expect, family counseling, speaking to other BRCA testing participants, support groups, and speaking to pediatricians and psychologists. Similarly, Segal and colleagues (2004) reported that mothers testing positive for BRCA1/2 mutations endorsed follow-up counseling sessions devoted specifically to disclosure, family counseling, peer support groups of carriers and their children, educational forums for families, and printed materials about disclosure, as valuable resources.

While health-care professionals or other resources may be needed in a supporting role, disclosing genetic risk to children is generally viewed as a parent's responsibility (Forrest et al., 2003; Forrest Keenen et al., 2005; Klitzman et al., 2007). If a parent refuses to inform children, this can lead to family rifts later on when adult children discover their risk for themselves (Klitzman et al., 2007; Petersen, 2006). In some families, some members may believe it is important to inform relatives (e.g., nieces or nephews) about risk, but communication may not occur since people do not feel they have the "authority" to override a parents' decision to not inform children (Keenan Forrest et al., 2005; Klitzman et al., 2007; Peterson et al., 2003). In this way, perceptions of disclosure authority can act as a communication barrier. Sometimes, however, people feel their responsibility is discharged when they inform their siblings, even if they do not go on to inform nieces and nephews (Gaff, Collins, Symes, & Halliday, 2005).

Family Communication Style

Just as individuals differ in their coping styles, families may have open or closed communication styles more generally, and these styles also influence communication about genetic risk (Metcalfe et al., 2008; Wilson et al., 2004). In general, families with open communication styles appear more likely to communicate about the family's genetic risks. In contrast, families with closed communication styles appear more likely to experience difficulties talking about genetic risks (Holt, 2006; Klitzman et al., 2007; Metcalfe et al., 2008).

There has been relatively little work on the identification and measurement of family communication styles in the context of genetic risk (Kasparian, Wakefield, & Meiser, 2007). Family communication about genetic risk has largely been studied with qualitative methodologies, making it difficult for researchers to adopt comparative study protocols or to generalize across diverse diseases and populations (Kasparian et al., 2007). In one exception, guided by family communication theory, Koehly and colleagues (2003) reported that in families undergoing testing for hereditary colon cancer, those with higher levels of cohesion were more likely to discuss genetic risk and testing options with their relatives. Models of family functioning suggest that highly cohesive families often have more open communication patterns (Olson, Russell, & Sprehkle, 1989).

Holt (2006) suggested that an analysis of family communication patterns be incorporated into clinical genetics assessment, to the benefit of both families and counselors. Research confirms that parents report difficulties in talking about genetic risk with children (Clarke et al., 2008; Hamilton et al., 2005; McAllister et al., 2007; Metcalfe et al., 2008), and some patients would value professional support and guidance in talking about risk information in their families (DeMarco & McKinnon, 2007; Gaff et al., 2005; Segal et al., 2004; Tercyak et al., 2007). These findings raise questions about the type of support that may be required for test candidates as they negotiate the difficult process of communicating with family

members about test results and the family's risk. Facilitating family communication about genetic risk is not currently a formal goal of genetic counseling (McAllister et al., 2007). While genetics clinics often provide family letters upon request and encourage clients to contact them should their relatives have questions, genetic counseling normally leaves the dissemination of family risk information to the test candidate. However, if an outcome of clinical genetics services is to promote individual and familial well-being and coping following genetic testing, clinicians must find ways to assist families with communication about genetic conditions (McAllister et al., 2007).

There are a variety of additional resources beyond family letters that may be beneficial to families in communicating about genetic risk. For example, support groups have been used successfully with high-risk women to provide psychological support and educational information (DeMarco & McKinnon, 2007). Supportive-expressive group therapy also improved psychological functioning in BRCA mutation carriers, although this intervention did not address disclosure issues specifically (Esplen et al., 2004). DeMarco and McKinnon (2007) also described retreats and web-based supports that may be valuable information resources. Intervention research that evaluates a variety of disclosure tools and resources is a priority area for future research on family communication of genetic information.

Family Myths About Inheritance

Richards (1996) described family myths – mistaken beliefs about disease inheritance within the family – that can cause inaccurate risk perceptions and act as barriers to communication. Common lay beliefs, for example, are that a disorder may skip a generation and may present only in one sex or only in first-born children (Richards, 1996). These beliefs affect who in the family may be told (van den Nieuwenhoff et al., 2007) or for whom the risk information is considered relevant (e.g., it may not be relevant to boys or to second-born children). Richards (1996) noted that such beliefs may serve a psychological defense function in families as they cope with knowledge of a genetic disorder in the family.

Similarly, family members may "pre-select" which member will be the one to develop the family illness, often based on similarity to an affected parent or grandparent; this is commonly observed in HD families (Evers-Kiebooms & Decruyenaere, 1998), but has also been observed in HBOC families (Wilson et al., 2004). Beliefs about who will develop the illness may have implications for family communication in that family members who have not been pre-selected may not be informed about the family risk.

Sociocultural Factors

Gender

Richards (1996) noted that women are likely to play the role of "kin keepers," taking responsibility for their families' health, including genetic

risk. In families affected by HD and HBOC, for example, women were more likely than men to collect family health information and records and to seek genetic testing (Forrest Keenan et al., 2005; Richards, 1996). d'Agincourt-Canning (2001) reported similar results in her interviews with families at risk for HBOC. While both male and female participants perceived a duty to share risk information with family members, only women assumed responsibility for widespread disclosure to include distant relatives. Men restricted their communication primarily to spouses, children, and siblings. In the case of HBOC, the gendered nature of disclosure is unsurprising given that breast cancer is largely a female disorder and women are more likely to be tested than men (d'Agincourt-Canning, 2001). d'Agincourt-Canning (2001) notes, however, that women may bear an undue emotional burden, feeling an obligation to share risk information with others, some of whom they do not know or from whom they are estranged. The gendered nature of disclosure may also impede disclosure of HBOC risk information to male relatives for whom the risk information is in fact relevant (Forrest Keenan et al., 2005; MacDonald et al., 2007; Wilson et al., 2004). However, in relation to HNPCC and IHC, which affect both genders equally, males and females appear just as likely to share risk information, at least with close relatives (Peterson et al., 2003; van den Nieuwenhoff et al., 2007).

Concerns About Genetic Discrimination

Guttmacher and Collins (2003) suggested the most commonly expressed fear about genetic information is that it will be used in ways which are detrimental to people; for example, to deny them access to health or life insurance, employment, or education. Across a range of disorders, insurance concerns are cited as an important reason to avoid taking a genetic test (Barlow-Stewart & Keays, 2001; Hall & Rich, 2000). Hall and Rich (2000) noted that fear of potential discrimination was especially acute in people at risk for late-onset disorders, such as HD. Their interviews with genetic counselors revealed that adults seeking testing for late-onset disorders had high levels of concern about potential discrimination, in sharp contrast to prenatal and pediatric counseling clients. Whatever the reality of the situation (Billings et al., 1992; Barlow-Stewart & Keays, 2001; Hudson, Rothenberg, Andrews, Kahn, & Collins, 1995), anxieties about potential discrimination represent real concerns for individuals at risk for a genetic disorder and act as communication barriers in families. In general, these anxieties inhibit or delay disclosure because people want to protect relatives from potential discrimination (Etchegary, 2007; Forrest et al., 2003; Wilson et al., 2004). This perception may change as countries introduce legislation to protect against genetic discrimination. For example, the Genetic Information Nondiscrimination Act of 2008 (GINA) (Genetic Information Nondiscrimination Act, 2008) prohibits health insurers from denying coverage or charging higher premiums to a healthy individual based solely on a genetic predisposition to a disease. GINA also prevents employers from using individuals' genetic

information when making hiring, firing, job placement, or promotion decisions. GINA does not apply to individuals affected by symptomatic genetic disease. Bearing in mind that it appears to be fear of potential discrimination, not necessarily actual experience or empirical evidence, it will be some time before it is possible to judge whether the existence of laws such as GINA reduces anxiety and promotes information sharing within families.

Culture

Some research suggests that lay constructions of family and kinship may influence people's perceptions of genetic risk, genetic testing, and disclosure practices (Forrest et al., 2003; Wilson et al., 2004). Thus, perceptions of "what" and "who" is considered "family" influence communication patterns and sense of responsibility for disclosing to certain relatives (Forrest Keenan et al., 2005; Wilson et al., 2004). Wilson and colleagues (2004) note that since constructions of the family are inherently social, they may not correspond with geneticists' and others' views of family relationships, nor for which relatives the genetic risk has implications. Both the culture and the ethnic context will likely influence perceptions of "family," along with attitudes toward genetic testing and the confidentiality of genetic information (Wilson et al., 2004), all of which are likely to affect disclosure practices.

This aspect of communication has received relatively little attention, and Gaff and colleagues (2007) note the lack of diversity in studies of family communication, most of which have involved participants of Anglo-Saxon or Anglo-Celtic background. The importance of exploring this subject in more diverse populations is illustrated by the work on cultural understandings of cancer, genetics, and family in a population of Chinese–Australian patients (Eisenbruch et al., 2004; Yeo et al., 2005; Barlow-Stewart et al., 2006). Barlow-Stewart and colleagues (2006) noted the importance of the notion of patrilineal descent in the construction of kinship, such that asking about "close relatives" might miss information about relatives on the maternal side (not considered to be as close as paternal relatives); another product of this notion is that first cousins on the paternal side might be considered by a consultand to be sisters and brothers, because they share a surname. Eisenbruch and colleagues (2004) also discussed how traditional Chinese beliefs could shape ideas of inheritance and disease causation, even in highly acculturated individuals. Their data revealed a pervasive belief in the notion of disease as a form of ongoing family punishment and shame for the bad behavior of an ancestor. This study also underlined how innocuous language used by professionals could be interpreted negatively by patients; for example, the specific term "faulty gene" can play into notions of bad luck, punishment, and shame and act as a barrier to open discussion of the situation within a family. The findings of these studies underscore the limitations of research in communication which is limited to particular ethno-cultural groups.

FUNCTIONS OF COMMUNICATION

A key feature of most social interaction and interpersonal relationships is communication (Bandura, 1977). It serves any number of functions, including a purely instrumental function that serves to convey information, to a normative function through which appropriate norms of behavior and belief are conveyed (Festinger, 1954). Communication in families also serves similar functions (Koenig Kellas, 2005), and in essence, the very functions of family communication can themselves act as barriers to, or facilitators of, genetic risk disclosure.

To Convey Information

One of the basic functions of communication is to convey information. In genetic risk communication, the function is to provide risk information that is perceived relevant for other family members, particularly for their own risk management decisions. A large literature confirms that many people are motivated to undergo genetic testing in order to provide risk information for family members (d'Agincourt-Canning, 2001, 2006; Hallowell et al., 2006; Klitzman et al., 2007; Wilson et al., 2004). While some individuals may encourage relatives to be tested, others simply convey the risk information, along with the possibility of counseling and testing, but refrain from persuading family members to get tested (Mesters et al., 2005). Either way, the basic function served by the disclosure is to convey information, and it is a facilitator of family communication about genetic risk.

Alternatively, this function may serve as a barrier to family communication if the information to be conveyed is controlled in either its timing or selectivity. As an obvious example, parents may withhold some or all of the information about the family's risk from their children until it is the "right time" to disclose (Clarke et al., 2008; Forrest et al., 2003; Metcalfe et al., 2008; Wilson et al., 2004). And as noted, people can be selective in what information they convey to relatives (Hamilton et al., 2005; Klitzman et al., 2007). In general, the selective nature of disclosure often functions to protect relatives from emotional distress or concerns about discrimination (Metcalfe et al., 2008; Wilson et al., 2004). However, holding back information undermines autonomy of decision making in those who are "protected." Further, in families with more closed communication, retrospective accounts of now adult children revealed feelings of guilt, fear, and resentment that had not been discussed with parents (Metcalfe et al., 2008).

There may also be differences in exactly what type of information is being conveyed to relatives and for what purpose. For example, a recent study found two different stages of disclosing genetic risk information to relatives (Forrest, Curnow, Delatycki, Skene, & Aitken, 2008). Across a range of genetic disorders, information was first relayed to relatives in the crisis stage immediately following the diagnosis of a genetic condition in the family. In this instance, the function of the disclosure was simply to convey the terrible news, rather than convey information about relatives'

own risk. Thus, at the time of diagnosis, the focus is on the diagnosed family member and the health implications of the condition. In the subsequent post-diagnosis phase, further communication with family members continued. The function of this communication shifted to warn relatives of the implications of the diagnosis for themselves (i.e., their own increased risk).

To Facilitate Coping

Another function of family communication about genetic risk is to help a person cope with abnormal genetic test results or the family's risk in general. An example of the latter is the phenomenon of pre-selection, noted earlier. In this way, family members select who in the family will go on to develop the family illness, and risk communication is influenced by this selection (Evers-Kiebooms & Decruyenaere, 1998). It has been suggested that communication with close female relatives may be a strategy used to cope with abnormal genetic test results (DeMarco & McKinnon, 2007; McGivern et al., 2004). Indeed, a recent study found that 70% of female participants reported the need for emotional support as a key motivation for disclosure after BRCA mutation testing, compared to only 34% of male participants (Finlay et al., 2008).

Similarly, McGivern and colleagues (2004) reported that participants discussed feelings about their test results more often with female relatives than male relatives; a widely reported finding in the literature (DeMarco & McKinnon, 2007; Wilson et al., 2004). Differences in the mode of communication were also observed, such that female relatives were almost always informed in person, while male relatives were informed over the phone, in person or through indirect communication with another family member (McGivern et al., 2004). Thus, the coping function served by family communication acts as a facilitator of disclosure of genetic risk and may also have implications for how risk is communicated. Research confirms that disclosure may also have positive psychological effects in that it has been shown to lower levels of distress and enhance personal relationships (DeMarco & McKinnon, 2007; Gaff et al., 2005). More broadly, narrative research confirms that stories serve as an important mechanism for coping with difficult experiences (Koenig Kellas, 2005), particularly illness (Frank, 1998).

To Create or Maintain Identity

Related to the coping function, communication also serves to convey or construct both individual and family identities (Koenig Kellas, 2005). A large body of narrative research suggests that identity construction is a central function of communication, serving to create and evaluate the self, both in times of illness (Frank, 1998) and in the telling of family stories more generally (Koenig Kellas, 2005). "In short, family stories affect and reflect family culture by communicating who a family *is* – its norms, its values, its goals, its identity" (Koenig Kellas, 2005, p. 366, emphasis in original). It is reasonable to assume, therefore, that when a family talks

about genetic risk, it may also be attempting to define its identity, particularly in terms of the illness (Sobel & Cowan, 2000). For example, Gregory and colleagues (2007) observed that "a crucial aspect" of family communication about hemophilia was "that it concerned not only the facts and the practical management of the condition, but also the communication of family values about the condition and assurances that it could be dealt with" (p. 195). Richards (1996) described family stories about "proneness" for developing the inherited disorder based on resemblance to an affected relative. In this way, family members try to make sense of the pattern of observable disease in their family and cope with the illness (Richards, 1996). Kenen and colleagues (2003) observed family stories about women's family history of cancer which served to assist women in making sense of not only the pattern of cancer in their families but also their own individual risk. Stories about the family history of cancer served as both a facilitator of and a barrier to family communication. For example, when both male and female family members had been diagnosed with cancer, participants' stories reflected this history, and they understood the implications of inherited cancer risk for male relatives. When family stories centered on the "bad blood" on one side of the family, however, some participants did not understand that breast cancer risk information was relevant for male relatives (Kenen et al., 2003). Further, family stories also influenced the heuristics women used to interpret their risk, which may also have implications for risk communication.

The relationship between identity construction and communication may have psychological implications for children in particular. For example, McConkie-Rosell and Spiridigliozzi (2004) described parents' dilemma in communicating with their children about the genetic risk and its serious implications, while simultaneously trying to foster children's self identify and self-esteem. When details of the family risk are not shared until later in adulthood, children could be forced to re-think their self-identity at that time, having implications for life aspirations and decisions (DeMarco & McKinnon, 2007; Malpas, 2006).

FUTURE DIRECTIONS

It is notable that most published guidelines and recommendations for health-care professionals on the communication of genetic risk information appear to focus on nondisclosure, rather than on communication (for a recent review, see Forrest et al., 2007). There is a need for more comprehensive guidelines for genetics health professionals regarding the process of counseling clients about the familial implications of their test results and how best to share this information with other family members. Even in cases of known nondisclosure, there is a "lack of clarity about what individuals should reasonably be expected to do, and how professionals should respond when they are aware that communication within a family has failed or is blocked" (Gaff et al., 2007). Doukas (2003) advocated the use of a "family covenant" in which genetics providers work with consultands at an early stage to consider what information should be

communicated, what should remain confidential, and exactly what should be conveyed to whom – an "a priori negotiation of how privacy is to be respected in the family" (Doukas, 2003, p. 318). The family covenant is an innovative approach but has not been developed into a practical form which can be evaluated in clinical practice.

A special issue which requires further research attention is the communication of information to children about risk of late-onset disorders. Policy statements and guidance documents consistently advise against testing fetuses or minors for late-onset disorders which are not immediately life threatening, such as cancer (World Health Organization, 2003). The general view is that children should be allowed to make up their own minds about risk assessment and testing when they are mature enough to deal with the information. Duncan and colleagues (2005) conducted a survey of genetics professionals in several countries and found widespread agreement with this view and also documented 49 cases of testing for disorders which could have late onset in minors, 22 in children aged under 14. In the latter group, the parents made the request for testing in 82% of the cases, and only two of the children had been informed of their test result. This is an exception to the general situation about "nondisclosure," where a person's genetic risk is known to other family members but not to the individual him- or herself. In this case, the child's autonomy is challenged both by the testing decision, and by the non-communication of the result. Whether this is balanced by the value of the information provided by testing is not clear; Duncan et al. (2005) noted that only half of the families were followed up, so a realistic estimation of harms and benefits is lacking. Research and debate in this area is likely to be dominated by the question of the appropriateness of genetic testing in itself (Bloch & Hayden, 1990; Clinical Genetics Society, 1994; Marteau, 1994; American Society of Human Genetics BoD & American College of Medicine Genetics BoD, 1995; Michie & Marteau, 1996; Michie, 1996; Fryer, 1997), but the issues which ensue regarding communication and disclosure also merit specific attention.

Further to this, there is a notable lack of information resources and disclosure tools for parents and children that might assist with genetic risk disclosure decisions and practices. However, research indicates that a variety of resources would be well received (e.g., written materials about disclosure, family counseling, or talking to others who have participated in mutation testing; Segal et al., 2004; Tercyak et al., 2007). Tercyak and colleagues (2007) found that 78% of mothers were interested in accessing three or more resources. Thus, an urgent area for future research is the development and evaluation of resources specifically devoted to issues of communication about genetic risk, notably between parents and children, but also within the wider family.

There is also a need for research that takes family members (i.e., the potential recipients), as opposed to probands (i.e., the potential communicators), as its focus; such research would be particularly valuable to inform the ethical and legal considerations about duty to warn. Only limited research has studied family members' perspective on this issue. In one study, people at risk for hereditary cancer from families with a known

HNPCC mutation were actively identified and contacted directly by health-care professionals (Aktan-Collin et al., 2007). Half of those contacted agreed to participate ($n = 286$), and of these, 51% and 40% participated in genetic counseling and testing, respectively. Notably 92% approved of the direct contact, and nearly all were satisfied with their decision to participate. In addition, no legal action or adverse reactions were observed in the original consultands or their relatives. Aktan-Collan and colleagues (2007) concluded that active recruitment of at-risk people may work well, particularly in countries where registries are readily available to facilitate recruitment. Other research with family members with a known HNPCC mutation also found strong support for the notion that all family members should be informed about the identified mutation in the family (Pentz et al., 2005). Most also indicated that it was permissible for health-care professionals to inform family members about their risk, with some noting that professionals could help overcome barriers to communication in the family (such as emotional or geographic distance or a consultand's refusal to disclose). However, some participants did distinguish between the right to share news of a genetic mutation in the family and the right to confidentiality of individual test results, thus upholding individual privacy considerations (Pentz et al., 2005). These studies provide rich insights into the contentious issue of the role of health-care professionals in the disclosure of genetic risks; however, there is a dearth of research in this area to make firm recommendations.

As the number of available genome-based tests increases, the issues around communication and disclosure may become more prominent. This may become evident as the focus shifts from genetic testing for risk of rare, highly penetrant, Mendelian disorders to "profiling" individuals according to groups of genetic variants believed to underlie disease susceptibility (Khoury, 2003). The individualized assessment based on a person's genomic profile is more likely to be quantitative (percent risk) than binary ("high risk"/"low risk") and will likely be mediated by lifestyle and environmental factors. This complexity will offer challenges to comprehension and probably make meaningful communication with family members more difficult.

The prioritization of personal privacy over a duty to warn at-risk relatives will be increasingly challenged as the ability to intervene in disease processes improves. The increase in genetics knowledge is producing more evidence about gene–disease associations, and DNA-based tests, than about the utility of the resulting genetic information in prevention of morbidity or mortality (Khoury, Millikan, Little, & Gwinn, 2004). Currently, there are few genetic conditions where lack of knowledge of risk status is life threatening and where effective interventions exist to prevent serious harm or death. Some forms of hereditary cardiac arrhythmias provide an example of the exception to this: the presenting symptom can be sudden death, potentially preventable with medication or implantable defibrillators (Hodgkinson et al., 2005). Increasing ability to intervene effectively to alter the outcome of serious disorders will challenge the balance between the duties of protecting privacy and warning relatives; at some point, the

debate will re-emerge about individual or family ownership of, and access to, genetic information (Lucassen, 2007).

Overall, a positive approach to promoting family communication is part of effective counseling for individuals, in terms of minimizing the harm to the consultand from anxieties surrounding communication and disclosure; the main route to promoting the well-being of the broader family at risk is also through the decisions and actions of individual consultands. Effective counseling requires an appreciation of the wide range of factors which promote or hinder effective communication of genetic risk within families and a willingness to explore these at an individual level. Discussions about communication and disclosure are appropriately broached as part of pre-test counseling, both in terms of understanding general family issues which are relevant to the consultand (e.g., anxieties about causing worry, family myths, cultural issues) and also in relation to context-specific issues (e.g., potential revelation of non-paternity, unacknowledged adoption). Consultands have a right to make disclosure decisions for themselves, and counselors have a duty to protect their privacy. However, both consultands and counselors have a duty to others in the family who may be at risk, and counselors are expected, at the very least, to ensure that consultands are made aware of this. There is a reasonably widely held view that non-directive counseling is inappropriate when the well-being of other family members is a matter of concern. Some people may need help with communication, and it is in keeping with the genetic professional's role to offer practical assistance, for example, by providing a letter for dissemination, by being available to disclose the risk information to at-risk relatives, or by facilitating referrals of relatives to colleagues, when they live at a distance. As noted earlier, counselors could also make clients aware of any support groups in their area, as well as refer them to known printed or web materials that may facilitate disclosure.

In conclusion, genomic information is essentially family information, and most people who learn about their own genetic risk are willing to share information with family members. Communicating genetic information raises awareness of risk in relatives, so that they may seek counseling and clarification of their own status, although each person also has a right not to be forced to learn about their own risk. Policies in most jurisdictions prioritize the protection of individual privacy over the disclosure of genetic information to relatives without the consultand's consent, but most also allow for overriding this duty in exceptional circumstances. While such circumstances are currently rare, this may change as more effective interventions to prevent or ameliorate the impact of genetic disease become available.

Finally, communication is a process not an act, is not always straightforward, and is not always complete or accurate; it is influenced by a complex interplay of factors pertaining to the individual, the condition, the nature of the risk information, and the family and broader sociocultural context. As the nature of clinically relevant genomic information becomes more complex, the challenges for effective communication within families should be anticipated.

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8

Conveying Genetic Risk to Teenagers

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With the mapping of the human genome and the rapid discovery and application of new technologies, recent years have brought about unprecedented advances in genetics and genomics, the latter being defined as "the study not just of single genes, but of the functions and interactions of all the genes in the genome" (Guttmacher & Collins, 2002, p. 1512). In the foreseeable future, it is expected that predictive genetic tests will be available for as many as a dozen common conditions (Collins & McKusick, 2001). For example, strides have been made in the discovery of genetic and genomic markers for such diseases as asthma, diabetes, certain cancers, and heart disease (Altshuler et al., 2000; Bell, 2004; Bottini, Musumeci, Alonso, Rahmouni, Nika et al., 2004; Malerba & Pignatti, 2005; Ober & Hoffjan, 2006; Palma, Ristori, Ricevuto, Giannini, & Gulino, 2006; Sogaard, Kjaer, & Gayther, 2006; Wooster et al., 1994). Results of genetic testing for these common disorders will be used to inform, often in individuals with family histories of the disorder, their chance of developing the disease and as a consequence what steps can be taken, if any, to minimize or eliminate future harm.

To date, results of genetic testing have been disseminated to adults because the process of understanding risk is often difficult for the general public (Weinstein, 1999) and may be especially so for youth. These challenges must be overcome if future genetic testing is to be performed with youth, for example, to motivate them to engage in preventative and self-protective behaviors in light of learned risk information. Overall, because findings of genetic polymorphisms may have risk implications for other family members, it is important that all relatives, including youth, for whom the test result has implications, are adequately informed of their risk of developing the disease.

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This chapter discusses potential methods for communicating genetic risks to adolescents. It begins with a brief discussion as to how youth, including adolescents, perceive illness causality and for whom discussions of genetics may be most appropriate. Next, it examines some of the challenges that would be inherent in conveying risks to adolescents, followed by the essential components of what it means to understand risks and important outcomes related to risk communication processes.

Because probabilistic information is often transmitted numerically (e.g., percentage, frequencies), this chapter discusses the concept of numeracy, its various functions, and suggested practical methods of communicating numeric risk estimates. At the end of the section on numeracy, the review includes the use of graphical displays as adjuncts in conveying numerical probability information, followed by details of other approaches that rely less exclusively on probabilistic information and more on the antecedents and consequences of risk (Rothman & Kiviniemi, 1999). This chapter concludes with recommendations for future research in this nascent area of decision and behavioral science.

ILLNESS PERCEPTIONS: THE ROLE OF CAUSALITY

Helping youth understand the multitude of risk factors that contribute to the etiology of common diseases, in order to encourage preventive behaviors and self-protective actions, is a daunting task. One key challenge is how to best convey the complexities involved in describing gene–gene and gene–environment interactions. How youth interpret and act upon these messages depends, in part, on their causal beliefs about illnesses.

Youth go through different developmental phases in determining causality for disease. Several studies have classified developmental processes in disease causality as closely resembling the stages of cognitive development originally proposed by Piaget (Bibace & Walsh, 1980; Perrin & Gerrity, 1981; see Burbach & Peterson, 1986, for review). In general, the earliest explanations of illness causality are based loosely on immediate contiguous or spatial cues, with increasing differentiation of internal and external causal factors, culminating in more concrete and abstract notions of how external agents of disease become internalized to produce illness.

One illustration is a classic study by Bibace and Walsh (1980). Via coding of interviews with youth aged 4–11 years regarding how the common cold occurs, the researchers found evidence for three broad categories of explaining disease causality: (1) prelogical, (2) concrete-logical, and (3) formal-logical. The prelogical stage (roughly ages 2–6) was divided into two domains: (1) phenomism, in which the child attributes the cause of illness to an external, concrete event that may coincide with the illness but is spatially or temporally remote (e.g., the sun did it), and (2) contagion, in which illness is due to objects or events close to, but not touching, the child or "magic."

The concrete-logical stage (roughly ages 7–10) was divided into two subcategories. In the first, contamination, children attribute the cause of

illness to touching a harmful external agent or by engaging in acts that produce harmful effects (e.g., violating rules of conduct such as not wearing a coat when it is cold outside). In the second, internalization, children begin to link how an external cause becomes internalized to produce illness (e.g., swallowing or inhaling). Although children now associate illness within the body, they maintain confusion about internal organs and their functions. A critical development in this phase is that youngsters now begin to differentiate between internal and external processes of disease and the mechanism through which external agents (e.g., germs) become internalized (e.g., inhaling); further, single or multiple causes of diseases may be given that allow the beginning of a rudimentary understanding of interactions between causal factors (Pidgeon, 1985).

In the formal-logical stage (ages$\geq$11), diseases are seen as due to physiologic and psychophysiological processes. Diseases are increasingly explained by malfunctions in a series of internal physiological mechanisms (e.g., blood circulation) and/or organs, as well as how psychological processes (e.g., stress) may contribute to disease. Symptoms are seen as being due to physiological malfunctions (Perrin & Gerrity, 1981).

By understanding children's explanations, belief systems, and lay models of disease causality, this provides an important backdrop in which to consider how one might communicate with young people about genetic illness. Specifically, these developmental phases have links to, and implications for, risk communication processes. For example, thematic discussions about gene–gene and gene–environment interactions may be appreciated most strongly among youth in the formal-logical phase of development. Further, youth at that phase are more likely to have a fuller appreciation of how the body functions; as such, the relevance of genetics and environmental causes to specific types of disease can potentially be illustrated. When there is greater knowledge about the link between internal and external causes of illness, it is possible that youth may come to exhibit a greater sense of control over the disease occurrence (Burbach & Peterson, 1986); this is key if the fundamental rationale for conveying genetic risk information to young people is to encourage primary prevention. Paradoxically, though perceived control may facilitate preventive behaviors (e.g., "I know I can do something about it."), it is also related to reduced perceived likelihood of harm (Klein & Helweg-Larsen, 2002). In sum, those who wish to communicate with youth about genetic risks need to be sensitive to developmental phase. Messages need to be framed accordingly and in terms of causal beliefs exhibited during a particular phase or else run the risk of promoting misperception and misunderstanding about the role of genetics in health and illness.

CHALLENGES OF CONVEYING RISK TO YOUTH

From a developmental perspective, a central question pertaining to risk communication is whether or not youth possess adequate cognitive capacities to understand and apply probabilistic concepts such as the ability to compute magnitude estimates, the ability to use frequencies, and the ability to understand concepts related to causality (discussed

in the preceding section). For example, key issues in the application of probabilistic concepts are how conceptions of probability develop from the preoperational stage of cognitive development (i.e., grasping concepts of cause and effect) to the concrete operational stage of cognitive development (i.e., engaging in the mathematics of probabilities) (Inhelder & Piaget, 1958).

The evidence thus far suggests that older children and adolescents are quite capable (and often more adult-like in their thinking than they are given credit for) to grasp and perform probabilistic tasks, especially when potentially interfering or extraneous information that can hinder task performance is eliminated or held to a minimum (see Reyna & Brainerd, 1994; Reyna & Farley, 2006, for reviews). What remains largely unknown, then, is whether or not communication approaches targeted to adults that concern health risks could or should differ from risk communications that focus on youth.

At the most basic level, this question centers on whether adolescents process, interpret, and use risk feedback in fundamentally different ways than do adults. Insights into these processes can be gathered by comparing developmental differences in risk-taking behaviors (for example, using abusive substances, engaging in unprotected sexual activities, and driving while under the influence) between children, adolescents, and adults. As summarized by Reyna and Farley (2006, p. 29)

> Compared to adults, children and adolescents have been found to be less able to delay gratification, inhibit their behavior, plan for or anticipate the future, spontaneously bring consequences to mind, or learn from negative consequences; and adolescents do not view consequences as being harmful as adults do, especially if the risk behaviors are engaged in only 'once or twice.' Children and adolescents also behave more impulsively (beyond individual differences that may linger into adulthood) reacting to immediate temptations without thinking, and discounting future rewards more heavily than adults do; and their goals evolve in predictable directions that promote healthier long-term outcomes.

These constellations of findings can affect various outcomes related to risk communication. Consequently, there are several challenges that need to be considered when targeting risk messages to adolescents – many apply equally well to adults. These challenges are described in greater detail below.

Time perspective: Several common diseases like heart disease, cancer, and diabetes most commonly occur during the middle years of life or during older age. Youth may question, both implicitly and explicitly, the saliency of concern about distal health problems and consequences when compared to current and proximal life events (e.g., finishing school, dating, and tasks related to their identity development). It is expected that for many youth, distant negative health events will be viewed in the abstract and with little embellishment of what it means to live in these disease states (e.g., how people who are affected by the illness think and feel about

it, how it is coped with). Such abstractions of disease may attenuate the perceived likelihood of disease occurrence (Trope & Liberman, 2003). A challenge in risk communication, therefore, is making potential adverse distant events more personally relevant to teens – perhaps by varying time perspective.

Enhancing the saliency between genetic risk and disease. Perceptions of risk and the actions that may be taken to avert harm are influenced by experiences around adverse events (Weinstein, 1989a). Overall, because most genetic polymorphisms related to common disease rarely elevate a person beyond moderate risk, gene–environment interactions take on a more prominent causal role. Consequently, for common diseases, if a family member does not experience the disease in question, it may lower youth's perceptions of the significance of genetics in the causal attributions of risk. However, should the event occur, the important question is what level of attributable risk does an adolescent assign to genetics as well as environmental causes of disease?

This illustrates the need to better understand how youth mentally construct prototypes of someone who is affected with a genetically linked disease – the closer the youth match this image, the more at risk they may be prone to feel (Gibbons & Gerrard, 1995) – as well as how they perceive elements of the disease process. This may be captured, for example, in their perceptions of illness or mental models of the disease in question (Morgan, Fischhoff, Bostrom, & Atman, 2002; Leventhal, Brissette, & Leventhal, 2003; Leventhal, Leventhal, & Cameron, 2001). As mentioned earlier, youth in the formal-logical phase have a deeper appreciation for internal and external causes of health and behavior and interactions among them. As such, educational efforts during this period of development may be crucial to teach and reinforce the concept of gene–environment risk factors for common diseases that could be incorporated in their illness prototypes.

Adolescents may dismiss communications that aim to affect their perceived vulnerabilities if these communications do not adequately address elements deemed important in the disease process, including genetics. Indeed, as Walter and colleagues argue, "differing senses of vulnerability to different diseases will influence the way people respond when health professionals discuss disease risk, particularly when lay and professional models of vulnerability differ" (Walter, Emery, Braithwaite, & Marteau, 2004, p. 593). This suggests that more effective communication of genetic risk information requires that health professionals explore their patients' understanding of the meaning of genetic inheritance and the underlying reasons for their sense of vulnerability to disease.

Aura of invincibility. Though adolescence is generally characterized as the healthiest stage of live, many youth maintain the highly optimistic (and, of course, unrealistic) belief that negative events are more likely to happen to others than to themselves. This can serve to lower their motivation to change risky behaviors in favor of healthier ones. Youth, nonetheless, both overestimate observed probabilities for life events and provide accurate predictions of life events (de Bruin, Parker, & Fischhoff, 2007; Reyna & Farley, 2006). This optimistic bias is pervasive across

several events, especially those that are perceived as being more controllable (e.g., being fired from a job, getting divorced after 5 years of being married; Weinstein, 1980; Klein & Helweg-Larsen, 2002).

Several cognitive and motivational mediators have been postulated for the optimistic bias (Weinstein, 1989b; Weinstein & Lachendro, 1982) and approaches to curb this bias have met with difficulty (Weinstein & Klein, 1995). Importantly, however, youth do not seem to possess a stronger aura of invincibility than do adults (Beyth-Marom, Austin, Fischhoff, Palmgren, & Jacobs-Quadrel, 1993; Quadrel, Fischhoff, & Davis, 1993), and this suggests that adult-targeted interventions for overcoming this bias may have similar effects on youth.

UNDERSTANDING OF AND OUTCOMES RELATED TO RISK COMMUNICATION

Risk is a difficult concept to convey and is poorly understood by the public (Fischhoff, 1995, 1999; Weinstein, 1999). A comprehensive understanding of risk requires individuals to know the precursors (e.g., risk factors) of possible harm, likelihoods of experiencing harm, and the pros and cons of preventative actions and their consequences (Weinstein, 1999). Teenagers, then, should understand the basic meaning of these four components of risk.

Most attention in risk communication is focused on conveying probabilistic information, perhaps due to the greater inherent complexities involved in describing uncertainty for possible events than in describing risk factors, consequences, etc. (Bogardus, Holmboe, & Jekel, 1999). A critical issue in the success of these communications is whether health experts, who are at the forefront of communicating genetic information to patients or the public, conceptualize and build their communications on the framework of what it means to understand a risk. Relatively few guidelines exist on evaluating the efficacy of risk communications (Edwards & Elwyn, 1999; Rohrmann, 1992; Weinstein & Sandman; 1993). Below is a summary of a few important outcomes that are used to evaluate the efficacy of risk communication processes. These could be considered as important when communicating genetic risk to adolescents.

- *Engagement in recommended behavior(s)*: A risk communication is deemed effective if perceptions of risk lead to health protective or disease prevention behaviors. A risk communication is ineffective or detrimental if it causes the person to act in a manner contrary to the broader health message, such as a decision of a young person to continue smoking cigarettes due to genetic feedback that expressed less susceptibility nicotine addition or lung cancer risk.

At times there may be no consensus as to what actions a person should take to avoid risk – such as when the benefits and risks are approximately equal, or when there may be no clear, consistent evidence of benefit or harm existing in a change of behavior. In these situations, the focal outcomes may be whether the person understands

the risks versus the benefits, makes a decision that is consistent with his/her values, is satisfied with the decision reached, and decreases possible feelings of regret should the decision lead to poor outcomes (Edwards & Elwyn, 1999).

- *Paying attention to the message*: A key factor in any communication is whether the target audience pays attention to the message. Risk messages that are attended to, as reflected in such outcomes as amount of information processed and reviewed, recalled, used, and disseminated to others, can be considered effective in some situations. This suggests that methods that engage youth in the active learning of genetics and outcome of genetic testing (e.g., more engaging and interactive activities, vivid displays that capitalize on natural curiosities, and tendencies toward self-exploration) may be more effective than methods that passively disseminate information (e.g., pamphlets).
- *Acquisition of factual knowledge*: Did the risk communication result in greater understanding of the phenomenon in question, especially in relation to the dimensions of understanding risk previously discussed (e.g., knowledge of personal risk factors, understanding what actions to take to reduce or prevent the negative outcome, understanding the nature of the disease/event, understanding probabilities of an event occurring)?
- *Effects on emotions*: Risk communications can cause undue positive or negative emotional reactions. For example, after receipt of risk information, individuals may express heightened anxiety, stress, or anger or they may (conversely) express unexpectedly high levels of positive affect in the context of probable negative outcomes. Emotional responses can have important consequences in terms of decision-making processes, behaviors, and perhaps psychological well-being (e.g., do the resulting negative emotions from the risk communications, if sustained, lead to persistently negative mood states?). Newer models of risk and decision making, such as risk as feelings (Loewenstein, Weber, Hsee, & Welch, 2001) and the affect heuristic (Slovic, Peters, Finucane, & Macgregor, 2005) suggest that emotions do play important roles in decision making.
- *Judging perceived risks/benefits*: Assuming that individuals are aware of actions that can be taken to reduce their risk of harm, they may understand neither the benefits and costs of such actions (e.g., stopping cigarette smoking to reduce the chance of developing smoking-related illnesses, but experiencing discomfort from symptoms of nicotine withdrawal) nor the benefits and costs of inaction (avoiding nicotine withdrawal, but persisting in smoking and increase the risk of premature morbidity and mortality). In addition, individuals may have difficulty balancing the possible outcomes of their decisions (how much is my risk reduced in light of the possible side effects?).
- *Evaluation of the messages*: To what extent does the audience find the information to be credible, accurate, useful, relevant, comprehensive, trustful, and clear and easy to understand? Whenever possible, these issues should be assessed. Some issues, like judging of perceived risks and benefits of action and the evaluation of messages, are important

mediators and moderators that can affect what the public health community considers to be of primary interest: behavior change. Naturally, variations in content and format of transmitting risk messages will affect the above outcomes differently, as (for example) the use of numeric probabilities.

PROBABILISTIC APPROACHES TO CONVEYING RISK: THE ROLE OF NUMERACY

A good amount of effort in conveying risk information is devoted to increasing the public's appreciation of the probabilities of harmful events occurring, such as the chance of developing heart disease as a consequence of an unhealthy diet. This chapter focuses on numbers to convey probabilities because of their widespread usage for this purpose (e.g., absolute risks, relative risks, attributable risks conveyed via percentages, frequencies). Because people have difficulties understanding and applying mathematical concepts, numeracy is obtaining significant attention in the health arena (Ancker & Kaufman, 2007; Fagerlin et al., 2007; Golbeck, Ahlers-Schmidt, Paschal, & Dismuke, 2005; Nelson, Reyna, Fagerlin, Lipkus, & Peters, 2008; Reyna & Brainerd, 2008). Admittedly, mathematical aptitude on standardized tests among children and adolescents in the United States lags behind other countries, although scores are improving (Reyna & Brainerd, 2007). Due to limitations in mathematical aptitude, one can argue that strategies involving the use of numerical risk information are likely to fail, which would be true if numeracy skills were used primarily to solve and interpret numerical data. Research and theorizing in numeracy supports six separable functions of numeracy in health decisions (Lipkus & Peters, 2009).

I. *Numeracy facilitates computation*: This dimension refers to specific skills needed to perform mathematical operations, including knowing how to seek information and what material to extract in order to perform these operations (Ancker & Kaufman, 2007), as well as knowing when a mathematical computation is needed. These operations can range from doing simple math, such as addition, subtraction, multiplication, and deciding on magnitude, to more complex problems like calculus, statistical inferences, and performing a trade-off of risks and benefits to make a medical decision.

For example, individuals may need to determine relative and absolute risks and how they differ from baseline levels. In decision making, some decision science tasks (e.g., standard gambles) require multiplying the objective/subjective probabilities of events with their outcomes to derive the "best" solution from among several options. In other settings, individuals may need to perform mathematical computations to perform trade-offs, such as calculating the expected benefits and risks and deriving a net degree of risk or benefit (e.g., weighing across different health events the absolute risks versus benefits of performing a preventive action). In terms of conveying genetic risk information, this

dimension would require imparting necessary skills to adolescents in order to enable them to make such computations.

II. *Numeracy encourages more information seeking and greater depth of processing*: Separate from computation ability, this second functional value of numeracy involves the motivation to seek and attend to numerical health information. It is believed that this dimension is separate from the motivation to seek out and attend to general health information (Hibbard, Peters, Slovic, & Tusler, 2005). When people are presented with numerical information, some review it in a cursory manner, if at all, while others process it in depth, making sure numbers are accurate, making comparisons between numbers, performing mathematical operations, etc. For example, when confronted with numerical data in a print advertisement, does the person try to process the data or skip it? Conversely, when no numerical data are given, some individuals will actively seek this information, such as when a person considering taking a genetic test asks for numerical data to determine his/her chances of developing a given disease. Indeed, people often want numerical data when faced with important decisions, perhaps because numerical data is seen as precise and obtained through scientific means (Lipkus, 2007).

III. *Numeracy improves interpretation of the meaning of provided numbers*: This dimension refers to the ability to make sense of numerical information to reach a decision or solution. As indicated within the risk communication literature, the attempt to understand numerical information is often indexed by personal estimates of risk that match some external criterion, and conclusions are derived from logically following that criterion.

In the medical decision-making literature, the above would be indexed by making a decision that maximizes expected or subjective utility. An example of the former would be whether after receipt of health-related feedback an adolescent provides a subjective estimate of her genetic risk that matches an "objective" estimated risk as derived by several existing algorithms (i.e., if told the risk is 3%, does she state 3%?). An example in decision making is making a choice between two options and selecting the option that is most likely to maximize expected utilities.

IV. *Numeracy facilitates assessments of likelihood and value*: Numeracy can affect the reliability and validity of self-report quantitative measures (Schapira, Davids, McAuliffe, & Nattinger, 2004). As a result, it also affects the meaning and utility of such measures. Oftentimes, persons are asked to answer probabilistic questions like "What is your chance of developing disease *X* on a scale from 0 to 100%?" Less numerate individuals may have difficulties not only in understanding the question but also in making use of response options or providing a numerical estimate as part of an open-ended question. If so, it is questionable whether their responses can be interpreted as meaningful. Consequently, it is essential to conduct developmental research to assess how well adolescents both use and interpret numerical probability scales. This is important given that there are no "gold standards"

of assessing perceptions of health risks (Diefenback, Weinstein, & O'Reilly, 1993).

V. *Numeracy increases acceptance of numerical data*: This dimension involves whether the recipient accepts as valid the processes contributing to the production of quantitative information and/or the conclusions reached from it. Some individuals may comprehend numerical data, yet discount the credibility of the source. They may also discount how the information and its form (e.g., percentages, frequencies) was obtained or used to derive a conclusion. For example, adolescents may not agree with their personal estimates of genetic risk if they feel the methods used to calculate the risk are based on assumptions they find questionable. Though this level of critical thinking (or consumer skepticism) may be more characteristic of adults, it is certainly possible to teach these skills to young people and they may generalize to other settings and circumstances in their lives.

Numerical estimates provided from sources that are perceived as less credible may be viewed as suspect. For example, some people view doctors and large health organizations as trusted sources, while others do not. Even with information from a generally trusted source, the conclusions reached may be viewed as flawed due to technical elements.

VI. *Numeracy promotes behavior change*: This dimension suggests that numeracy may affect the motivation to take action and engage in behaviors based on quantitative information (e.g., someone who may be genetically more susceptible to disease may take action to curb their risk). Numeracy may either increase or decrease the likelihood of action following some quantitative message, perhaps through one or more of the functional values discussed: information seeking, computation, interpretation of meaning, etc.

As the preceding functions suggest, how one conveys numerical genetic risk data may need to be individually tailored to an adolescent's numeracy skills. Ideally, risk messages should be conveyed in a manner that facilitates understanding while inducing little cognitive effort on the part of recipients, thereby increasing the likelihood that these messages will be effective. Below are some suggested ways of enhancing the communication of numerical risk that aim to foster solid understanding (Lipkus, 2007; Paling, 2003).

STRATEGIES IN THE USE OF NUMERICAL DATA TO CONVEY PROBABILISTIC RISK INFORMATION

- Be consistent in the use of numeric formats. For example, do not compare percentages with odds or frequencies. Make comparisons among similar, rather than different, objects.
- Use the same numeric denominator (e.g., compare 5 out of 100 with 15 out of 100).

- Round numbers and avoid the use of decimals (Covello, Sandman, & Slovic, 1988). Individuals understand more readily wholes than wholes-plus-parts (e.g., it is easier to grasp 30 than 29.6; Brase, Cosmides, & Tooby, 1998).
- Risk perceptions vary based on whether communications using ratios that differentially or equally emphasize the numerator (which often represents the number of individuals affected) and the denominator (which often represents the total population at potential harm). In general, the literature is inconsistent with respect to whether individuals pay more attention to the numerator or the denominator (Halpern, Blackman, & Salzman, 1989; Yamagishi, 1997). Where the emphasis is placed – on the numerator or on the denominator or on both the numerator and the denominator equally – is what may decide which aspect is attended to most. The resulting impression of risk is likely to be influenced by such placement of emphasis (Stone et al., 2003; Stone, Yates, & Parker, 1997).

The expressions of mathematically equivalent ratios present their own challenges and may result in varying perceptions of risk (Reyna & Brainerd, 2008). For example, according to the ratio-bias phenomenon (Alonso & Fernandez-Berrocal, 2003; Denes-Raj & Epstein, 1994; Denes-Raj, Epstein, & Cole, 1995; Pacini & Epstein, 1999), expressing a ratio as two smaller numbers (e.g., 1 out of 10) leads to lower perceptions of event likelihood than the same ratio incorporating larger numbers (e.g., 10 out of 100). Even though both are mathematically equivalent to each other, conveying a ratio using the latter format may increase the perceived magnitude of risk.

- Numbers close to zero (e.g., 1% or less) may be dismissed as representing no risk. Events that are perceived as well understood, familiar, and less severe may be more readily dismissed than events that are more poorly understood and viewed as more consequential (Verplanken, 1997; Fisher, MCClelland, & Schulze, 1989). If the idea is to stress some level of risk, regardless of how small, a message to this effect is in order ("Even though the risk is extremely low, it may still happen.").
- Communications of relative risk state the risk is "*X* times" higher than another ("If you are susceptible to disease *Y*, your chance of getting a disease is twice as likely compared to those found not to be susceptible."). This often results in an overestimation in perceived risk (Covey, 2007; Edwards, Elwyn, Covey, Matthews, & Pill, 2001; Moxey, O'Connell, McGettigan, & Henry, 2003). If the goal of the communication is to achieve a more accurate assessment of risk, one must specify the relative risk and include the baseline value. ("The chance of individuals found not to be susceptible to disease *X* is 1%, while those found to be susceptible is 2%; therefore the chance of getting the disease is doubled among susceptible versus nonsusceptible individuals."). Including base rate information often reduces the perceived risk (Covey, 2007; Natter & Berry, 2005), and including it along with relative risk has been recommended for conveying risk data (Edwards, Elwyn, & Scott, 1999). For the issue as to when people attend to base rates, the reader is referred to the review by Koehler (1996). Again,

basic research on adolescents in this context is sorely lacking but highly needed.

- Many health communications use percentages to convey relative risk. Informing individuals that they have a certain percentage greater or lesser risk is vague (e.g., "Those who took the medication reduced their cholesterol 14% compared to those who did not take the drug."). To make the comparative percentage more meaningful, specify the baseline risk value (e.g., "On average, the risk is 5%. Your risk may be 10% higher, that is, 5.5%" – or, to simplify, around 6%.).
- Avoid having adolescents undergo complex calculations (Waters, Weinstein, Colditz, & Emmons, 2006). Simplify the calculations, be explicit about how to conduct the calculation, or provide a summary of the result(s) with some discussion of what the result means (e.g., "When we add your two risk factors, lack of physical activity and your genetic makeup, your risk is 2 out of 100; that is, among 100 people like you, we expect that, on average, two will get heart disease by the time they turn 50, assuming that they continue to be physically inactive.").
- If a specific action or interpretative standard/threshold exists in relationship to a numeric risk value, provide it. For example, if average risk represents a value of 1 out of 10,000, inform the target audience that values above this threshold involve greater than average risk, along with any recommendation for action. Good examples of such communications exist for environmental risks (e.g., radon; Sandman, Weinstein, & Miller, 1994; Sandman & Weinstein, 1994).
- If possible, avoid using logarithmic scales, which are poorly understood by the populace. For example, it is generally difficult for laypeople to fathom how a risk of 1 in 1,000,000 is that much different than a risk of 1 in 100,000 – most do not experience these events, and adolescents are even less likely to have experienced rare events. However, there have been suggestions to use logarithmic scales, such as the Pauling Perspective Scale (Paling, 1997; Stallings & Paling, 2001). A study on blood transfusion risk comparing this scale with a written numerical form using a "1 in *X*" format revealed no differences in knowledge about or in perceptions of transfusion risk (Lee & Mehta, 2003).

The success of these numeric strategies to inform the public about probabilities of harm is often manifested in two ways. The first approach assumes understanding by an existing match between the provided numerical estimate and the individual's estimate, although there may be several reasons why a match does not occur (Lipkus, in press). The second approach suggests that there is an understanding when the individual correctly ranks the order of events from least likely to most likely to occur.

The utility of these strategies can also be judged in other ways to evaluate the efficacy of risk communications (for example, do people at the same level of risk behave similarly) as well as in relations to the outcomes mentioned earlier (e.g., evaluations of the message) (Weinstein & Sandman, 1993).

Of critical importance is the inherent meaning that youth derive from the numerical information provided. Indeed, while computed or derived probabilities may be incorrect, an individual may take away the correct interpretation. For example, if a probability is close to zero, the important message is that while the likelihood of the event occurring is low, its occurrence is still possible. If need be, summary statements describing main take home message should accompany such information. These messages should be communicated in plain/lay language to foster better understanding.

THE USE OF GRAPHICAL DISPLAYS AS ADJUNCTS TO CONVEYING NUMERICAL PROBABILISTIC RISK INFORMATION

Numbers, despite their strengths, have several limitations (see Lipkus, 2007, for review); therefore, an alternative and complimentary strategy of conveying risk magnitudes is to use graphical displays (see Ancker, Senathirajah, Kukafka, & Starren, 2006; Lipkus & Hollands, 1999, for reviews). Graphical displays are especially effective in conveying relative risks and changes in risk by capitalizing on basic perceptual processes. Early on, children are able to make automatic perceptual estimates of relative magnitude of visual objects that can inform probability judgments (Reyna & Brainerd, 1994; Reyna, 2008). Graphic displays may be one mechanism to convey relative risks to children.

A method that is easily understood by even very young children is to show them spinners (Reyna & Brainerd, 1994). A spinner is, basically, a pie chart with an arrow originating from the center that can be spun. Once spun, it lands on a color-coded segment of the pie. The amount of area devoted to a colored segment represents the probability. For example, a pie chart can display a 25% chance of getting a disease by having a red-colored segment apportioned to 25% of the area, with the remaining 75% colored blue. Having youth visualize how often the spinner lands on the red segment provides an experiential account of the magnitude of risk. If the task is to compare two different probabilities (e.g., "Which one is more likely to occur, 40 or 60%?), two different spinners can be used to illustrate the relative magnitude of risk (see Reyna & Brainerd, 1994, Figure. 11.2).

Differences in relative risk can also be illustrated with histograms – the height difference between two or more bars provides perceptual information about differences in risk. Similarly, relative risk is conveyed well via the use of stacked bars whereby a single bar represents the frequency or proportion of people with or without a genetic alteration. Stacked bars are useful because they make the numerator and denominator more salient and hence help to avoid issues of denominator neglect – a contributing cause to overestimation of small risks and confusion with conditional probabilities such as calculating sensitivity and specificity (Reyna, 2008). Venn diagrams might also be useful in clarifying nested classes of events that typify ratio judgments (i.e., whole-to-part relationships).

Risk ladders represent yet another tool that can inform relative risk judgments (Sandman et al., 1994). Events placed higher on the ladder – the ladder typically being a vertical scale – are assigned greater risk compared to events at the bottom of the ladder. Of import, risk ladders can denote when a risk crosses a threshold point demarcating when action might be needed, along with the specification of the action required. These action statements might be especially useful to youth who often have difficulty contemplating future events.

Finally, changes in risk over time are well captured by line graphs, which are often used in survival or mortality curves (Mazur & Hickam, 1994). For example, changes over time in the probability of being afflicted by a disease with or without a genetic origin can be graphed via two lines. Change in risk over time between these two conditions is inferred by differences in direction and slopes (Zikmund-Fisher, Fagerlin, & Ubel, 2007).

In sum, comparisons of risk magnitudes often aid in assigning meaning to inform risk judgments. Graphical displays, by capitalizing on automatic perceptual processes, can overcome some of the weaknesses of numerical information by making magnitude of risk comparisons more salient. This perceptual salience may be more easily retrieved from memory and more striking than the precise numerical values that often accompany risk messages. Additionally, graphics and pictures may be more appealing and engaging to young people.

INCORPORATION OF PROBABILISTIC INFORMATION WITH OTHER RISK COMMUNICATION APPROACHES

A potential weakness with conveying genetic risks that focus entirely on probabilities of harm, whether the probabilities are presented numerically or otherwise, is that they capture only one, albeit critical, aspect of what it means to "know a risk." A parallel approach to conveying risk is more contextual; contextual approaches focus on the causes, risk factors, and consequences of the disease (Rothman & Kiviniemi, 1999). Consequences include the psychological (e.g., emotions, mental well-being), social (e.g., effects on social relationships, such as level of social support, well-being on others), economic (e.g., costs of treatment), and physical (e.g., level of functioning; pain). Both risk factors and consequences are dimensions related to people's illness beliefs that shape perceptions of a disease (Leventhal et al., 2003). One can envision contextual approaches to risk communication as being specific instances of how to modify illness beliefs.

Contextual approaches may be more suited to conveying risk to youth than approaches that focus on risk probabilities. As mentioned, some youth have problems in spontaneously bringing consequences to mind, learning from negative consequences, and assigning equal amount of harm as adults to negative consequences (Reyna & Farley, 2006). Contextual approaches can address these shortcomings in risk judgments; probabilistic approaches do not. Moreover, as described below,

contextual approaches can illustrate the link between internal and external disease causes – especially gene–environment interactions – and may facilitate educational efforts bridging different stages in the development of disease causality, such as progressing from concrete to formal-logical thinking.

Helping adolescents understand how a risk factor, in this case genetics, contributes to the etiology of disease is inherent in the discussion of risk factor information. For example, how does a genetic mutation translate to increased risk and through what mechanisms are biological processes affected? Understanding the mechanisms through which a genetic alteration can affect risk (e.g., abnormal cellular replication, absence of producing a needed protein) may help pinpoint ways to lower risk by intervening in the causal chain, if possible. These efforts can indirectly affect perceptions of what can be done to avert and control risk, which is a dimension of understanding risk as well as an element of illness beliefs.

While there are no shortages of approaches to conveying risk factor information and the consequences of disease (flip charts, worksheets, videos, etc.; Rothman & Kiviniemi, 1999), one promising approach is to engage adolescents in the *active* learning of genetic information, such as through the use of science education. One of the major goals of science education is to help young people gain general science literacy so as to make more informed decisions about health, lifestyle, and societal issues. Regrettably, national samples of high school students rank low in science achievement relative to other developed nations (Takahira, 1998) and their achievement in science continues to decline (National Center for Educational Statistics, 2006).

Teaching science within the context of a topic that is already interesting to students increases the likelihood that students will learn (Kwiek, Halpin, Reiter, Hoeffler, & Schwartz-Bloom, 2007; Schwartz-Bloom & Halpin, 2003). Students are often exposed to issues of a scientific nature that impact their daily lives. Popular topics in high school biology classes include discussions of evolution versus intelligent design, the safety of herbal drugs, stem cell therapies, and genetic testing. At the University of Utah's Genetic Science Learning Center, strides are being made using science education to create modules that explain how genetics relates to our lives and society (www.learn.genetics.utah.edu). As a case in point, there is evidence that adolescents are becoming interested in the genetics associated with vulnerability to nicotine addiction (Tercyak, Peshkin, Wine & Walker, 2006).

Given the interest in and strides being made to identify genetic polymorphisms related to addiction (Bierut et al., 2007; Saccone et al., 2007), genetic testing for nicotine addiction may occur in the foreseeable future. To illustrate how we might communicate the processes of addiction and the role of genes to adolescents, we consider the case of the dopamine receptor gene *DRD2*, and dopamine transporter gene *SLC6A3*, that are among some of the most widely studied genes hypothesized to influence nicotine dependence (Lerman et al., 2003; Stapleton, Sutherland, & O'Gara, 2007; Swan et al., 2005).

In addition to any classroom training, a multimedia science education module can be loaded onto a laptop computer. The theme of the module would focus on nicotine addiction as a disease that is similar to other chronic relapsing diseases, such as hypertension or type 2 diabetes. Individuals are not born with these illnesses; rather, they emerge when a person with a certain genomic profile is exposed to an environmental trigger such as smoking or high-fat diets. The educational module would have three sections that cover the following topics concerning nicotine addiction:

- *Nicotine pharmacology or "how nicotine works"*:
  - Nicotine binds to "nicotinic" receptors (proteins) all over the brain to change electrical activity.
  - In the midbrain, nicotine binds to receptors and causes the release of dopamine, which is responsible for pleasurable effects (called the "reward pathway") and desire to seek cigarettes.
  - Nicotine produces other effects such as increased alertness, decreased anxiety, and appetite.
- *Key cellular events in the development of nicotine addiction*:
  - The ability of nicotine to release dopamine in the reward pathway is important.
  - Dopamine released at the midbrain dopamine synapse binds to dopamine receptors such as *DRD2*; this underlies reward and pleasure (see Figure 1).
  - Dopamine action is terminated by binding to dopamine transporters such as *SLC6A3* on the releasing neuron (see Figure 1).
  - With repeated exposure to nicotine, nicotinic receptors become less sensitive and alter their number.
  - Changes in nicotinic receptors underlie tolerance and dependence on nicotine; these usually precede addiction (represented by craving when nicotine is not present).
  - With repeated exposure to nicotine, dopamine release becomes reduced; this explains craving and the attempts to increase dopamine release by smoking more.

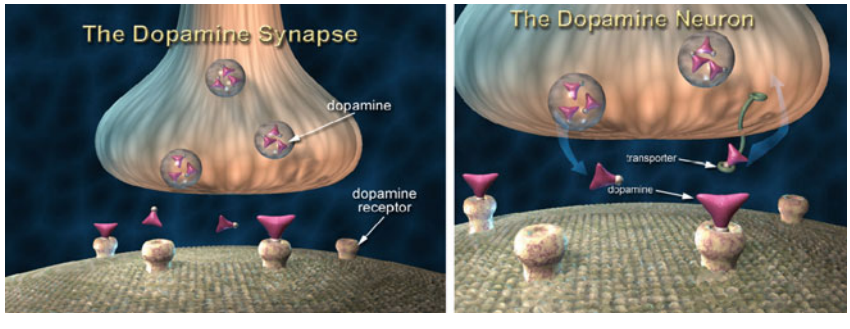

Figure 1. Typical dopamine synapse containing the protein products (the dopamine receptor and transporter) of the DRD2 and SLC6A3 genes.

- Onset of tolerance, dependence, and addiction varies with the individual (e.g., their genetics).

- *Genetic factors*:

  - Several gene polymorphisms may contribute to the risk of developing nicotine addiction; focus in on two examples of proteins (dopamine receptor and transporter) that play a role in addiction.
  - People who carry different forms of the dopamine (a neurotransmitter) receptor gene or the dopamine transporter gene can experience stronger craving for nicotine leading to difficulty quitting; having both genetic alterations is additive.
  - People who carry a form of the dopamine receptor gene and/or the dopamine transporter gene respond differently to nicotine cessation drug therapies.

The module would contain illustrative 3-D graphics showing the action of nicotine at the cellular level (Figure 1). The pictures could depict a typical dopamine synapse containing the protein products (the dopamine receptor and transporter) of the *DRD2* and *SLC6A3* genes, respectively (i.e., the markers of interest). Following the presentation, participants can be asked questions to assess their basic understanding of the information (e.g., What are the roles of the *DRD2* and *SLC6A3* genes? What is the level of risk associated with having polymorphisms in *DRD2* and *SLC6A3* genes?).

This science education approach capitalizes on *active learning*, whereby the learner acquires new knowledge through interesting and current interactive activities; interactive activities are postulated to promote greater elaboration of the information, therefore facilitating the active construction of new knowledge (Kalyuga, 2007). This compares to *didactic learning*, whereby the learner more passively acquires knowledge through listening and/or reading materials. It has been suggested that an active learning approach is more effective for learning abstract scientific concepts, including issues of genetic risk, by helping to create and reinforce mental models (i.e., knowledge structures) than didactic approaches (Dede, Salzman, Loftin, & Ash, 1997; Kaphingst et al., 2009). Given advances in interactive technology, active learning can be facilitated through the use of immersive environments, such as virtual reality.

Virtual reality has several advantages as a potential science education tool (Blascovich et al., 2002; Kaphingst et al., 2009; Persky & McBride, in press). First, it allows the educator to create a realistic portrayal of the environment of interest while affording a high degree of experimental control by manipulating the critical factors that persons experience. Second, it allows the educator to manipulate factors that would be immutable, invisible, or intangible. For example, one can change characteristics of the person, such as height and weight, and create artificial environments that could not be experienced (e.g., becoming part of a human cell). Third, virtual environments allow the educator to capture distinct behaviors

that would be difficult to capture in real-life settings, such as nonverbal behaviors (e.g., visual gaze).

Virtual reality can be used to illustrate how the dopamine receptor works. In this case, youth can be made to feel they are on a dopamine receptor and examine the range of activities that occur (e.g., update and release of dopamine) and how these may differ as a function of different genetic polymorphisms (Blascovich et al., 2002). Similarly, they can envision being transported on a protein molecule and experience the myriad of events that take place to learn more directly how proteins affect certain outcomes.

Immersive environments could also be used to simulate outcomes related to genetic testing, such as the deliverance of test feedback. An avatar (or artificial likeness of an individual) can be created of the adolescent, a health professional, parents, and the interactions modeled. The interaction can simulate the result of being told that one is more or less genetically susceptible to a disease, demonstrate how this is explained, and obtain reactions to the information and feedback. Further, given that the future of genetic testing will entail testing several genetic markers for risk of disease (i.e., multiplex testing) it would be useful to use similar simulations for providing explanations for and feedback about several markers of risk. For example, assuming that there are four markers of genetic risk for disease, how do adolescents react to being told they have an elevated risk based on one to four markers? These virtual approaches carry some advantages over more traditional analog approaches to education, such as case scenarios, vignettes, stories, or imagined outcomes because they enhance the salience, look, and feel of the entire experience for those involved.

SUGGESTED AREAS FOR FUTURE RESEARCH

There are seven suggested areas of research that can help fill gaps in our knowledge pertaining to risk communication of genetic information to youth – many of which are applicable to adults as well.

Conceptualization of genetics. Both qualitative and quantitative research is needed to achieve a better grasp as to how adolescents understand genetics and its role in the etiology of disease. This will help to identify mental models of genetics and diseases that can be used as part of educational materials. For example, insights can be gained pertaining to knowledge gaps and misperceptions of genetics and disease. Additionally, it is necessary to have a better appreciation of how teens come to value the purposes and the outcomes of genetic testing.

Understanding the role of familial and peer influence on risk perceptions. Adolescent health behaviors (such as diet, physical activity, and tobacco and alcohol use) are oftentimes socially mediated and influenced by familial and peer networks. Similarly, how adolescents will come to interpret and use genetic testing feedback may depend, in part, on the family members' reactions and attitudes toward genetic information and subsequent risk implications. For example, parents and peers who

discount the importance of genetics as causal factors to disease in relation to other known risk factors may cause adolescents to adopt this view, attenuating any positive effects the feedback may have on behavior change. A topic that merits further study is how conflicting reactions from family and peers are negotiated. Clearly, how and to whom genetic testing information is conveyed continues to be an important yet understudied area. It is likely to become even more important should genetic testing among young people proliferate.

Integration of genetic information with other risk factors. Multiple risk factors contribute to common diseases. An issue to consider here is the extent to which providing adolescents with genetic test findings detracts or enhances their focus on other disease risk factors, especially as a function of the result. For example, non-genetic risk factors may become more important when the test result reveals higher risk. By assigning more importance to these non-genetic risk factors, the adolescent may achieve greater perceptions of control via other avenues to affect disease risk. Conversely, if an adolescent attaches extreme causal importance to genetic risk factors upon being told of his/her higher risk status, feelings of fatalism may ensue and may cause the adolescent to discount other risk factors that do play a critical role in the etiology of disease.

Testing for multiple genetic alterations creates unique and challenging scenarios in and of themselves, as well as challenges for integrating this information with non-genetic risk factors. To simplify the situation, consider that a target audience can receive feedback about one or more genetic and non-genetic risk factors that can affect one or more diseases. This creates a 2×2 table, as shown in Table 1. Based on this classification scheme, under what scenarios will genetic feedback be given greater causal importance? One might predict that when the communication focuses only on genetics and when a specific alteration is related to more diseases, genetics will be seen as more causal in determining disease outcome than when couched with other risk factors focused on a single disease.

The main point is that if one is to provide a comprehensive assessment of risk, it will likely entail conveying more than just genetic information. How this is contextualized within this 2×2 matrix, when relevant, may significantly affect risk perceptions and resulting behavior change. Testing adolescents' reactions to feedback within each of these cells is valuable in helping to formulate the content of the risk communication.

Explore the role and interactions between gist and verbatim processing. People process information via two parallel systems: verbatim, which

Table 1. Classification Scheme Between Number of Risk Factors and Number of Diseases

Number of risk factors	Number of Diseases	
	One	More than one
One		
More than one		

focuses on the retention and use of facts provided (e.g., the risk that was given to me is 3.5%) and meaning derived from the communication (e.g., I feel my risk is low) (Reyna, 2008). It would be useful to understand the mental weighting that young people assign to verbatim information versus gist information when it comes to genetic risk and how the two are combined.

With increasing age, individuals rely more on gist than verbatim processing (Reyna & Farley, 2006). This raises the question of which approach to risk communication is more effective: stressing facts or stressing the meaning of those facts? A different but equally important issue is whether children, adolescents, and adults, who are given the same verbatim genetic risk information, interpret it similarly.

Insights into processes of motivated reasoning. People do not passively respond to health information. What they attend to and how they interpret it depends, in part, on their emotional states, their expectations at the time they receive information, and their motivations, of which two are key: accuracy and defensive motives (Chaiken & Trope, 1999; Chen & Chaiken, 1999; Kruglanski, 1996; Olson & Zanna, 1996).

Individuals motivated by accuracy process information open-mindedly and even-handedly to ensure that final judgments about a health threat are correct, while people motivated by defensive concerns strive to arrive at conclusions that support personally relevant and important beliefs (Chaiken, Giner-Sorolla, & Chen, 1996; Kunda, 1987, 1990).

Research on motivated reasoning and on resistance to persuasion provides insights into the types of reactions recipients of threatening genomic information may have. These include (a) minimizing threat by downplaying disease severity, (b) viewing negative test results as common (i.e., normalizing the threat), (c) questioning the accuracy of the test (Kunda, 1987, 1990; Croyle, Sun, & Hart, 1997; Ditto, Munro, Apanovich, Scepansky, & Lockhart, 2003; Liberman & Chaiken, 1992), (d) generating counter-arguments or other unfavorable cognitive responses, (e) expressing anger or irritation, or (f) failing to attend to all of the information (Brock, 1967; Kruglanski, 1996; McGuire, 1964; Petty, Tormala, & Rucker, 2004; Tormala & Petty, 2002; Zuwerink & Devine, 1996). These motivated reasoning reactions may be especially likely among people who feel they cannot avert the threat or who feel that no effective strategies exist (Janis, 1967; Leventhal, 1971; Rogers, 1983; Witte, 1998).

It would be very useful to explore the extent to which motivated reasoning processes occur in response to genetic testing, to assess young people's short- and long-term effects on risk perceptions and health behavior change and to develop methods that can curb these reactions when they produce deleterious effects. As discussed earlier, curbing the optimistic bias, which can be considered a motivated reasoning outcome, has been difficult to change.

Efficacy of didactic versus active learning approaches. More work is clearly needed to ascertain under which conditions didactic versus active learning approaches facilitate learning about genetics – active learning seems beneficial to the learning of probability and statistical concepts (see Garfield & BenZvi, 2007; Sedlmeier, 1999, for reviews).

For example, Kaphingst and colleagues, in a highly creative experiment, tested two ways for adults to learn about genetic–environment interactions pertaining to a fictitious disease called "gallbladder hyperplasia" (Kaphingst et al., 2009). Using immersive technology, participants were placed inside an elevator that contained a row of buttons representing possible levels of genetic and behavioral risk factors. When buttons were pushed, the elevator would move either up or down and stop on a floor. When the doors opened, participants viewed how many virtual people entered a "hyperplasia" clinic. The floor at which the elevator stopped and the number of people entering the clinic both represented the degree of risk based on different combination of risk factors.

In the didactic learning conditions, participants listened to a lecture given by a virtual female health educator detailing how genetic and behavioral factors interacted to affect disease risk. Learning was facilitated by using screenshots from the virtual world to illustrate learning objectives using the elevator metaphor. Results were intriguing. While didactic learning was superior to active learning on some measures, for example, on recall, change in mental models and believability, active learning was superior on ratings of motivation, interest, and enjoyment. Whether the latter sets of findings encourage superior learning among children and adolescents remains to be seen.

Enhancing sensitivity to cognitive development of causal reasoning. As discussed, youth differentially progress through developmental stages of their understanding of disease causality. An important endeavor is to develop and assess the effects on understanding simple tools that parents and health providers can use to illustrate the causal role of genetics and the environment based on developmental stages.

CONCLUDING STATEMENTS

The future of genetic testing may target children and adolescents. Whether the provision of test findings will promote adaptive behaviors to curb disease remains to be discovered. In many ways, adolescents have the same skill sets and capabilities to process risk information as adults, and similarly, many of the challenges related to processes and outcomes related to risk found in adults (e.g., optimistic biases) apply to adolescents.

As with many risk communication approaches, whether the approaches are focused on probabilistic information delivered numerically, or on risk factors and disease consequences, their successes will depend on the format of delivery and, ultimately, the meaning the recipient derives from the information. It is hoped that the suggestions contained herein shed light on areas for future work, furthering the effectiveness of the communication of genetic risk targeted to youth.

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Part III

Genes, Behavior, and Health

9

Prenatal Screening and Diagnosis

KELLY E. ORMOND

INTRODUCTION

Deciding to and becoming a parent is filled with many emotional changes and challenges for the individual, the couple, and the broader family. When an individual or couple first contemplates parenthood, it is usually through the lens of society, their culture, religion, and family system. Despite some differences, in general parents hope for a healthy child, and even during pregnancy often begin imagining their child's entire life, from birth through adulthood. Undergoing prenatal testing as a part of the pregnancy process can potentially add an additional layer of complication that was not historically present – women, couples, and families now have the potential ability to learn some health information about their prospective child and have the ability to make decisions in light of that information. This context of genetic testing in the obstetrics realm is quite different from that performed in a pediatric setting (where one is providing testing as part of a diagnostic workup, usually for a child known or suspected to have a genetic condition) or from that performed in an adult setting (where one is testing oneself, often in a predictive manner).

Rather than focusing on a specific category of diseases, this chapter provides a short historical overview of prenatal screening and diagnosis and discusses what factors play a role in women's and couples' decisions about whether to undergo prenatal testing in general and some of the factors that influence what form of prenatal testing is selected. This chapter also discusses some of the more common psychological responses associated with the prenatal testing process and the potential impact of receiving unexpected news about the compromised health of the developing fetus, including "bad news," and the various decisions that may follow. The reader is reminded that all women, couples, and families react differently to pregnancy and the prenatal diagnosis process. The

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psychological aspects reviewed herein may vary widely, particularly for families from non-European countries versus families in the United States (where a majority of the data presented were derived). It is also worth noting that the vast majority of research regarding prenatal testing focuses on women, rather than the role of the spouse or partner; despite this, the partner should be considered, and their psychological responses to the testing process may be quite different from those of pregnant women.

HISTORY AND CURRENT STATUS OF PRENATAL SCREENING AND DIAGNOSIS

Prenatal diagnosis became available in the late 1960s and has been used to screen and diagnose a range of fetal conditions; some are inherited and others occur sporadically or due to a combination of genetic and environmental causes. Table 1 outlines the various forms of prenatal testing that will be discussed. There are forms of prenatal testing that focus on carrier screening of the prospective parents for recessive conditions on the

Table 1. Forms of Prenatal Screening and Genetic Testing

Form of Screen/Diagnosis	Invasive or Non-invasive	Conditions Detected	Time Performed
Genetic carrier screening	Non-invasive	Parental carrier status for conditions on the basis of family history or ethnicity	Anytime: preconception through pregnancy
Maternal serum screening	Non-invasive	Identifies pregnancies at increased risk for neural tube defects, and some forms of aneuploidy (Trisomy 21, 18). Not diagnostic; amniocentesis or CVS will be recommended	1st or 2nd trimester
Ultrasound	Non-invasive	Detects some, but not all, physical anomalies. "Soft signs" suggesting aneuploidy may require follow up through amniocentesis for accurate diagnosis	Detailed anomaly scan performed 18–22 weeks
Chorionic Villus Sampling	Invasive	Diagnostic for aneuploidy and other chromosome anomalies; can be used to test fetal DNA for specific conditions	10–13 weeks
Amniocentesis	Invasive	Diagnostic for aneuploidy and other chromosome anomalies; can be used to test fetal DNA for specific conditions. Also, neural tube defects and ventral wall defects	15+ weeks

basis of family history or ethnicity. Other forms of prenatal testing focus on screening the fetus directly and may entail noninvasive measures (such as ultrasound or serum screening) that identify fetuses at increased risk for conditions such as Down syndrome or neural tube defects (e.g., spina bifida or anencephaly) or invasive diagnostic tests (such as amniocentesis or chorionic villus sampling, CVS) that allow for diagnostic testing on the fetal chromosomes and DNA, as well as on various proteins or enzymes that may be present in the amniotic fluid.

Genetic Carrier Screening

Genetic carrier screening is typically offered for one of two reasons: a family history of an autosomal recessive or X-linked condition or based on ethnicity and offered for conditions that are more frequent in certain populations. Carrier screening on the basis of a family history can be quite a different process psychologically for patients, given that they (often) have personal experience with the condition in their family and may have more intimate knowledge of both the medical and the social aspects of living with the condition. Individuals may have known from a young age that they were at risk to be carriers or even known their own carrier status since childhood or adolescence. Alternatively, if a sibling passed away at a young age, parents may have difficulty discussing the genetic aspects with at-risk siblings, and consequently these individuals may have little information (or misinformation). Individuals can also develop preconceptions about whether or not one is a carrier, often based on common personality traits or physical features with other family members. Individuals who have a family history and are contemplating carrier screening can have significant feelings of guilt, shame, or blame and in many cases may decide not to undergo carrier screening at all (Botkins & Alegmagno, 1992; Fanos & Johnson, 1995; James, Hadley, Holtzman, & Winklestein, 2006).

Ethnicity-based genetic carrier screening began in the late 1960s with the advent of Tay Sachs carrier screening. Tay Sachs is a neurodegenerative condition that is fatal in early childhood; it is autosomal recessive and has an increased prevalence in the Ashkenazi Jewish population. As such, it served as a model for carrier screening public health programs in that it was a medically serious and untreatable condition that was relatively frequent (1/30 carrier frequency) and where biochemical testing accurately identified a high proportion of carriers with a low false-positive rate. Since that time, ethnicity-based carrier screening has expanded dramatically (Table 2; American College of Oncologists and Gynecologists [ACOG], 2000, 2001; American College of Medical Genetics, 2008). For all of the conditions currently included in testing, both members of the couple must be carriers in order to have an affected child. However, depending on the specific mode of carrier testing, some genetic tests may not detect all carriers of the condition, and patients may be left with a "residual risk" for carrier status and for having an affected child. This is particularly true for conditions where there is a common mutation in one population (e.g., within the Ashkenazi Jewish population) and a substantially lower sensitivity in testing individuals of other or mixed ethnicities. Since patients tend to perceive medical test results as binary ("I am a carrier" or "I am not

Table 2. Ethnicity-Based Screening Guidelines

Population	Condition(s) for Which Screening Should Be Offered	References
Caucasian (non-Jewish)	Cystic Fibrosis (CF)	ACOG (2001)
African American, Caribbean Hispanic, Mediterranean, Asian	Hemoglobinopathy screening (sickle cell, thalassemias)	ACOG (2000)
Ashkenazi Jewish	Tay Sachs, Canavan, Familial dysautonomia, CF, Niemann–Pick A, Fanconi anemia C, Bloom syndrome, mucolipidosis, Gaucher disease type 1	ACMG (2008); ACOG, 2004

a carrier"), this residual risk provision and its related uncertainty can create anxiety and confusion for couples where one member of the couple is a known carrier and test sensitivity is low for the other partner. Individuals' reactions to learning they are carriers of recessive conditions through ethnicity-based carrier screening often report feelings of surprise and disbelief since there is typically no family history of individuals affected with the condition.

While carrier screening can be performed preconception, it is most frequently performed during pregnancy, which can add to the complexity of prenatal decision making (Garber et al., 1993). Several studies have found low uptake rates of preconception genetic carrier screening when offered to members of the general population (Clayton et al., 1996), and it is thought that for most individuals, preconception ethnicity-based carrier screening is not seen as "relevant" and therefore not undertaken. Despite this, several successful preconception carrier screen programs exist within the Ashkenazi Jewish population, including Dor Yeshorim, a program within the Orthodox Jewish community (where arranged marriages are frequent) that tests participants and does not provide specific carrier results but rather alerts prospective couples as to whether they are "compatible" or not. Other studies have successfully offered genetic carrier screening to high school students (e.g., Clow & Scriver, 1977), but programs such as these raise questions about offering genetic testing to minors, including how such results may impact their self-esteem and self-image, and whether the results will be recalled correctly in the future. It is possible that the long history of genetic carrier screening within the Jewish community has led to increased awareness of the concept and greater acceptance of carrier screening when offered. The use of educational programs for carrier screening has been shown to improve the informed consent process (Hegwer, Fairley, Charrow, & Ormond, 2006) and is encouraged by professional societies (ACMG, 2008).

Non-invasive Screening in Pregnancy

There are several tests that can be performed in pregnancy that provide information about fetal health, but which do not pose a physical risk to the pregnancy – these typically include ultrasound and maternal serum

screening for biochemical markers that predict Down syndrome, spina bifida, and a range of other conditions (e.g., Smith-Lemli-Opitz syndrome, X-linked steroid sulfatase). It is important to remember that these noninvasive measures are, at least currently, *screening measures* and do not provide diagnostic information. Rather, they only select those pregnancies that appear likely to be at an increased risk on the basis of the markers analyzed and provide justification for couples to consider further diagnostic testing. A high percentage of those pregnancies that screen positive are unaffected, and this screening process can create anxieties for parents who are then faced with decisions regarding invasive diagnostic testing.

Ultrasound has expanded dramatically in the past 40 years, and clinicians are now able to perform imaging of the developing fetus to detect a wide range of physical birth defects. These can range from club foot to heart defects to lethal skeletal dysplasias. Some conditions are isolated and may be treatable via surgery (usually postnatal); others may be associated with broader syndromes and may have poor prognoses that include other physical anomalies and developmental disabilities. Ultrasound can also detect "soft signs" that are associated with conditions such as Down syndrome, but as a screening measure can only suggest which pregnancies are at increased risk. Ultrasound is a highly visual procedure that provides the opportunity for parents to "see the baby" and even receive photographs and videos of their potential child. This, especially in the first trimester, can increase parental attachment. It is unclear whether the level of parental bonding is related to the type and quality of information given to parents at the time of their ultrasound. Studies are also contradictory regarding whether three-dimensional ultrasound, which provides a more "realistic" fetal image, increases attachment compared to two-dimensional ultrasound (Sedgmen, McMahon, Cairns, Benzie, & Woodfield, 2006; Rustico et al., 2005; Righetti, Dell'Avanzo, Grigio, & Nicolini, 2005; Ji et al., 2005).

Maternal serum screening was first performed in the early 1980s, when elevated levels of alpha-fetoprotein (AFP) were newly associated with open neural tube defects including spina bifida and anencephaly; several years later lower-than-average levels of AFP were associated with Down syndrome. Since that time, maternal serum screening in the second trimester has expanded to include other analytes (hCG, inhibin, unconjugated estriol) and ultrasound nuchal translucency screening, and when performed in the first trimester it has a sensitivity of up to 86% for serum analytes alone and 95% when combined with nuchal translucency screening (Ball et al., 2007).

Invasive Diagnostic Testing

Starting in the late 1960s, amniocentesis became available as a way to determine fetal chromosome makeup. This development paralleled legal decisions such as Roe v. Wade (1973) and allowed couples the opportunity to undergo prenatal diagnosis with the option for legal pregnancy termination if a fetus was identified as affected with a disabling trait. Currently, chorionic villus sampling (CVS) and amniocentesis are available to provide

a diagnostic assessment of chromosomal anomalies (such as Down syndrome or other numeric or structural chromosome anomalies) or to assess the fetal DNA for specific genetic mutations. Oftentimes, in order to gain useful information about the developing fetus, a specific diagnosis must be under consideration. In the case of a family history of genetic disease, the knowledge of a family-specific mutation is useful in ensuring the most accurate results and interpretation. These tests can be performed between 10 and 13 weeks (CVS) or after 15 weeks (amniocentesis) and generally provide highly accurate results. Yet, they each carry a risk of miscarriage, typically estimated at 1/100–1/1,000 depending on the study, and other factors such as operator experience.

In past, only women at increased risk for chromosome anomalies based on age or an abnormal screening test (ultrasound or serum screening), or who had a known family history of an inherited condition, were offered invasive prenatal diagnosis. However, in recent years, health-care providers have acknowledged that while the risks of miscarriage and of having an abnormal fetus may be approximately equivalent numerically, patients assign different personal risks and meaning to these options (Kupperman et al., 2000; Grobman, Dooley, Welshman, Pergament, & Calhoun, 2002). More recent professional guidelines (ACOG, 2007) suggest that all women be provided both screening and invasive prenatal diagnosis options and encouraged to decide which option best suits their personal preferences. Trends suggest that as noninvasive screening increases in sensitivity, more women of all ages are opting to undergo screening measures first and then using the results to determine whether they undergo subsequent diagnostic testing. As discussed later in this chapter, this raises interesting questions when contemplating newly developing technologies in maternal serum screening that may provide diagnostic testing options (through free fetal DNA or other techniques) in a noninvasive manner.

FACTORS THAT IMPACT WHETHER TO UNDERGO PRENATAL TESTING

A number of studies have assessed which factors may be associated with the uptake of invasive prenatal diagnosis. The decision to undergo prenatal testing may be affected by various factors, such as the desire and timing of the pregnancy. For example, nearly 50% of pregnancies are considered unintended, either as an event or with regard to their timing (Finer & Henshaw, 2006). This complicates psychological adaptation to pregnancy by delaying attachment and adding ambivalence to the list of emotions that the couple will experience. Individuals may feel guilty for having mixed feelings about continuing the pregnancy, and when faced with the decisions surrounding prenatal diagnosis, particularly abnormal results, this can complicate decision making. Nowhere is this more salient than in adolescent pregnancy. Beyond this, 10–15% of all couples are considered infertile, which means that they have not conceived after a year of trying. For these couples, the path to pregnancy and parenthood

can be highly complicated and may involve treatment with medications that induce ovulation (and sometimes multiple gestations), or with in vitro fertilization and/or donor egg/sperm techniques. The psychological responses to infertility can be emotionally consuming and are beyond the scope of this chapter. Oftentimes, when couples who have undergone treatment for infertility learn that they have become pregnant, they discover that they have been so focused on the conception that they have given less thought to the remaining aspects of pregnancy and the future health of their child. For these couples, the pregnancy and impending parenthood becomes a highly sought after outcome; this may also be coupled with uncertainty over whether or not they will be able to conceive again in the future. As a result, they may be less willing to undergo any form of prenatal testing that results in pregnancy loss.

Ethnicity appears to play a role in uptake of prenatal screening, but this finding may, in part, be related to lower accessibility of adequate prenatal care in certain populations (Frisbie, Echevarria, & Hummer, 2001) or to differences in cultural and/or religious beliefs relating to inclination to terminate a pregnancy found to be affected with Down syndrome, belief that medicine or testing is interfering with pregnancy, or trust/distrust of the health-care system (Kupperman et al., 2006). Despite these findings, it remains critical that providers not stereotype women based on demographic factors, which might lead to inaccurate assumptions regarding desire for prenatal testing or screening.

As has been reviewed, prenatal testing is available in many different forms, each providing a different set of information, with different risks to the mother and fetus, and different sensitivities to the information obtained. In essence, prenatal testing is about obtaining information and understanding the potential contextual impact of that information (medically, psychologically) for the mother, couple, and family. Individuals and couples place different values on the various issues that testing raises. Negative results that convey information that the developing fetus is healthy can provide parental reassurance and facilitate attachment to the pregnancy, particularly when there is a family history of an inherited condition. Positive results that convey information that the developing fetus is at risk or unhealthy can allow parents the option to continue or terminate a pregnancy affected with a specific condition or anomaly. Parents continuing a pregnancy may also have time to arrange a special needs adoption if so desired and time to adjust and grieve before an infant's birth. Parents and couples will make decisions about undergoing prenatal testing based on a number of factors, including their empiric and perceived risk for having a child affected with a specific condition, their perception of the "burden" of raising a child affected with a specific condition, their perception of the potential risks inherent in prenatal testing, and their tolerance for uncertainty.

One of the many factors that can influence the parents' process of considering prenatal testing is anxiety. Pregnancy is a time when generalized anxiety is increased for a variety of reasons: fear of parenthood, fear of having a child with a birth defect, fear of procedures during pregnancy and of the birth process/delivery, fear of pregnancy loss, fear that one cannot get

pregnant (or get pregnant again), and fear of changing body image/other self-esteem issues. Anxiety in pregnancy is an important concept as it relates to the prenatal diagnosis process, in part because high levels of anxiety can impair cognition, memory recall, and attention, making complex decision making even more difficult. Anxiety can also alter risk perception and perceptions regarding the health of the baby and may play a role in motivating parents toward or away from prenatal diagnosis. In extreme situations, the prenatal diagnosis process can potentially impact bonding and attachment with the pregnancy. Barbara Katz Rothman's sociologic work calls this the "tentative pregnancy," in terms of delaying acceptance and bonding with the pregnancy until prenatal testing or screening results are available and the prospect of miscarriage and/or pregnancy termination is "resolved" (Rothman, 1993). Finally, it is controversial whether elevated maternal anxiety impacts maternal and fetal health.

Many studies have been performed to assess pregnant women's anxiety during pregnancy, both in general and in relation to prenatal testing and screening. It has been widely documented that women who have initial positive screening results on serum screening or ultrasound have elevated anxiety, increased even above women who have similar numerical risks based on maternal age (e.g., Abuelo, Hopmann, Barsel-Bowers, & Goldstein, 1991; Hoskovec et al., 2008). This elevated anxiety appears to decrease after an unremarkable ultrasound (Tsoi, Hunter, Pearce, Chudleigh, & Campbell, 1987) or amniocentesis (Marteau et al., 1992a).

Anxiety regarding invasive prenatal diagnosis appears to be related to both fear of the actual procedure (including the risk for miscarriage) and fear of the potential for abnormal results (Marteau, Johnston, Kidd, Michie, & Cook, 1992b). When women who underwent amniocentesis were compared to those who declined, researchers found that anxiety in both groups begins at similar levels, increases immediately before the procedure, and then drops after the procedure to levels similar to the pre-testing levels (Tercyak, Johnson, Roberst, & Cruz, 2001).

Some preliminary data also suggest that providing preliminary results from fluorescent in situ hybridization (FISH) reduces anxiety when normal results are present (Leung et al., 2001; Tucker et al., 1997) and that it does so more rapidly than waiting for final karyotype results (Ormond, Sturm, Grobman, & Shulman, 2005). But, most prenatal care centers offer FISH only if the patient is considered "high risk," such as a woman who is >20 weeks gestation or for whom an ultrasound anomaly has been detected. Studies suggest that when women are given a choice to undergo FISH, they elect it primarily because they are concerned about waiting for the results and that they hoped to receive reassuring information more quickly to decrease their worry. Additionally, they express concern about receiving "bad news" of an affected fetus (Sturm & Ormond, 2004; Sturm, Grobman, Shulman, & Ormond, 2005; Ormond et al., 2005). This suggests that women's perception of anxiety may be directly associated with the uptake of FISH if it is made available routinely.

It remains important that health-care providers consider the role of anxiety in pregnancy and recognize that it can be moderated by providing

patients with a sense of control and predictability, as well as providing support and coping resources. Several studies suggest that genetic counseling, which provides a combination of education and psychological support, can also reduce patient anxiety (Ruiz-Bueno, Sime, & Kitchell, 1991; Keenan, Basso, Goldkrand, & Butler, 1991; Ormond, 1997).

Even in the absence of counseling, women choose to undergo prenatal testing and screening for a range of personal and social reasons. Some women undergo testing because they want to know if a fetus has medical problems so that they have the option of pregnancy termination; such decisions may be based on their perception of burden related to the condition that is diagnosed, or for which they are at risk. Some women undergo testing because they desire reassurance and reduction of anxiety. Some have knowledge of an increased risk (due to maternal age, family history, or a positive screening measure) and desire "certainty" regarding the fetus' health. Others may be "information seekers" who want the test simply because it is medically available; these patients may also have increased risk perceptions and/or increased anxiety relative to other women. Some women may undergo prenatal testing because of pressure from their partners, families, health-care providers, and society. And finally, some women may not even realize that they are undergoing a prenatal screening test (most commonly a non-invasive test, such as maternal serum screen or ultrasound).

Women may decline prenatal screening and testing for a variety of reasons, including avoiding pain associated with the procedure, the potential to miscarry, an uncertain waiting period for the results, or the possibility of obtaining abnormal results. They may also choose not to undergo testing because the results would not impact decisions surrounding the pregnancy even if a fetus were found to be affected (either for religious or for personal reasons), although these women may still benefit from obtaining information and preparing emotionally before the birth of an affected child. Women may also feel they are "too far along" and attached to the developing baby and therefore do not want the information. Some women may not undergo testing due to lack of access or knowledge about test availability, the late timing of learning they are pregnant, or financial cost. Finally, others may decline invasive testing because they misunderstand the accuracy of the test, confusing testing with screening, having heard about the anecdotal woman "who had the test and it told her the baby had Down syndrome but everything was fine."

In contrast, many women appear to be less aware that noninvasive screening, such as ultrasound or serum screening, is being performed primarily to detect the potential of congenital anomalies or genetic syndromes, and in retrospect when faced with positive screening results, some women anecdotally report that if they had better understood this issue they would not have undergone the screening. For example, because ultrasound is noninvasive, most patients in United Stated have at least one during pregnancy, and this does not appear to increase anxiety. Many patients undergo ultrasound to learn fetal gender, "see the baby," or to "get pictures," which can lead to surprise when anomalies are detected. Women from lower income families have been found to be more likely to report

that they wanted to see the baby or obtain an ultrasound picture; higher income women were more likely to report that they underwent ultrasound to verify "that all was normal" and for reassurance (Gudex, Nielsen, & Madson, 2006). Women's interest in undergoing invasive prenatal diagnosis does not appear to be significantly impacted by ultrasound results, either for positive or for negative results (Vergani et al., 2002), suggesting that prior attitudes toward invasive testing are more important than screening results.

Other studies have assessed maternal serum screening internationally and found that women in the United States are significantly more likely to undergo maternal serum screening, proposing that the routine nature of screening has led to a decrease in informed consent among women in the states, as screening becomes more of an "opt out" procedure than one for which the woman must make an informed decision to undergo screening (van den Berg, Timmermans, Kate, van Vugt, & van der Wal, 2005). As serum screening has increased in sensitivity, and as first trimester screening has become more widely available, it appears that in some US populations more than 75% of patients offered maternal serum screening or combined first trimester screening will undergo it (Spencer, Spencer, Power, Dawson, & Nicolaides, 2003; Stenhouse et al., 2004).

Several studies suggest that women are more likely to proceed with invasive prenatal diagnosis if serum screening results suggest a high risk and that up to 80% of those found to be at high risk went on for invasive testing (Spencer, 1999; Dommergues, Taieb, Thalabard, & Frydman, 2001; Seror, Costet, & Aymé, 2001; Spencer et al., 2003). This rate appears to be lower if the woman is over 35 years of age and had previously expressed ambivalence about invasive testing (Mueller, Huang, Summers, & Winsor, 2005; Caughey et al., 2006) or if the elevated risk is "close to the cutoff level" (Spencer, 1999). It seems that women >35 years of age undergo maternal serum screening and/or nuchal translucency measurement to help them decide whether to undergo invasive testing (Weinans et al., 2000) and which test to undergo (Caughey et al., 2006), and that this approach decreases the overall amniocentesis uptake rate and increases the rate of uptake for noninvasive first trimester screening (Wray et al., 2005). In contrast, women <35 appear to undergo screening for reassurance (Weinans et al., 2000) and are therefore more anxious and more likely to undergo invasive prenatal diagnosis if the screening results suggest an increased risk. Finally, several studies (Geipel et al., 2004; Gjerris, Loft, Pinborg, Christiansen, & Tabor, 2008) suggested that fewer pregnancies conceived with assisted reproductive technologies undergo invasive prenatal diagnosis, and that such women are more likely to use ultrasound to decide whether to then undergo invasive testing. This may be due to a heightened sensitivity toward the risk of miscarriage and a high value being placed on maintaining a pregnancy which required significant effort to achieve.

Finally, there are a number of complicated social issues that may also impact psychological responses to prenatal testing and abnormal prenatal diagnosis. These include personal views about pregnancy termination, beliefs around disability and disease, state and national laws, and social pressures from family, friends, and caregivers.

THE GENETIC COUNSELING PROCESS

Women who are undergoing invasive prenatal diagnosis typically undergo genetic education and counseling as a mechanism of ensuring informed consent; this is usually provided by either a master's-level genetic counselor or their obstetrician. The content of these pre-testing discussions is highly variable, but may include a discussion of the risks and benefits of the procedure, information about the condition(s) for which testing or screening is available, the subsequent "accuracy" of the test or screening procedure (these make up the "genetic education" component), and ideally the incorporation of the patient or couple's personal values as they relate to the decision about whether to undergo prenatal diagnosis and hypothetical decisions if a fetus is found to be affected through testing. Perhaps partly as a response to the eugenics movement of the past, the profession of genetic counseling has developed a "nondirective ethos" (Kessler, 1997; Weil et al., 2006; White, 1997), implying that reproductive advice-giving should be avoided. However, there are little data regarding what is actually said during genetic counseling sessions, and some data suggest that there is variation among providers of different professional training backgrounds.

It has also been challenging within the research community to define successful outcomes after genetic counseling services, since measuring patient satisfaction, knowledge, or testing uptake do not necessarily convey that a "good decision" has been made. Several authors have proposed that measurements for informed choice (e.g., Marteau, Dormandy, & Michie, 2001a, 2001b) and decisional conflict (O'Connor, 1995) best reflect the success of the genetic counseling process. Both are similarly defined as including an understanding of the conditions for which testing is being performed, the test characteristics and implications, and that the process results in a decision that is consistent with the personal values. On the whole, these are important outcomes of the prenatal genetic counseling process that deserve additional thought and consideration.

In the past decade, there have been several studies that assess the use of patient decision aids, both in general medical decision making (e.g., O'Connor et al., 1999; O'Connor et al., 2003) and specifically to support prenatal diagnosis decisions (e.g., Bekker, Hewison, & Thronton, 2004; Nagel et al., 2008). These decision aids can take varied forms, ranging from written pamphlets, "slide shows," or videos, and more recently interactive computer or DVD modules. Some decision aids are focused primarily on medical facts, while others include an interactive component that allows patients to explore and clarify their own values and consider various options in light of these expressed values. A significant benefit of these approaches is the standardization of information and the ability to supplement the patient education process in a manner that is time efficient for the health-care provider and that may allow the patient to contemplate the various issues and their values in advance of when a medical decision needs to be made. However, in order for these decision aids to be clinically useful, it is critical that these decision aids are seen as a *supplement* to the existing health-care process, rather than a replacement for it.

Due in part to concerns over the variable content included in genetic counseling sessions, the 2008 passage and enactment of the "Prenatally and Postnatally Diagnosable Conditions Act" (PL-110-374) mandates that specific information be provided, "to increase the provision of scientifically sound information and support services to patients receiving a positive test diagnosis for Down syndrome or other prenatally and postnatally diagnosed conditions." It will be interesting and necessary to observe how, if at all, this federal legislation impacts the prenatal genetic counseling process as it occurs in various settings.

RECIEVING "BAD NEWS"AND THE SUBSEQUENT DECISION MAKING

Parents are sometimes faced with the unexpected diagnosis of fetal anomalies through prenatal diagnosis. Typically, once a diagnosis is made, parents are offered information regarding the likely prognosis for the child, possible referrals to specialists and/or families who have experienced a similar diagnosis, and (depending on the timing of the diagnosis and the laws of their state or country) they may be offered the option to continue or terminate the pregnancy. This communication of the diagnosis to parents is critical, as the manner in which it is conveyed and the information provided can significantly impact their perception of the condition and future decision making (Abramsky, Hall, Levitan, & Marteau, 2001), as well as the parents recollection of how the information and decision-making process occurred (Skotko, 2005a, 2005b). Regardless of the parents' decision, it is helpful to be honest, validate the parents' reactions, and work to create an individualized "plan" for the parents to create memories and process their grief (Green & Malin, 1988).

Psychological Reactions to Abnormal Prenatal Diagnosis

Parents can have a wide range of psychological reactions to learning abnormal prenatal diagnosis results. Many parents are in a state of shock and disbelief that the results could be correct. Beyond this reaction to receiving bad news (Buckman, 1992), the fetus can remain an abstract concept, and prognosis is often unclear or variable. Without the ability to "visualize" the outcome, it can be hard to move to a stage of accepting the accuracy of the results. The shock and anxiety that occurs at the time of diagnosis can also make it more difficult for parents to retain and process complicated risk and medical information. Parents can also experience feelings of guilt or blame themselves that they may have caused the fetal anomalies – often asking, "was it something that I/we did, such as having a diet soft drink or drinking a glass of wine before we knew we were pregnant?" While typically these are not the etiology of the condition, parents feel a combination of guilt and shame that they may have caused the anomaly, fear that the cause was uncontrollable and may happen again, and fear that they may never be able to have a healthy baby.

Parents also have a wide range of responses to the specific information regarding the condition that has been diagnosed, and this can be influenced by the information provided and the provider who communicates that information (Abramsky et al., 2001). The couple may or may not have undergone pre-procedural genetic counseling, and the information that was provided to the couple about the conditions for which they were at risk can be variable in its amount and content. Couples' prior personal experience with disability within their own families, communities, and as presented through the societal lens, will also influence their perception of the condition. Health-care professionals who provide additional information come to the communication process with their own experiences as well, with different views and approaches – no matter how "nondirective" the process is purported to be. Studies are increasingly assessing the linguistic content and presentation about the conditions for which screening or testing is offered. For example, Michie, diLorenzo, Lane, Armstrong, and Sanderson (2004) assessed the content of leaflets provided before amniocentesis. Few studies have prospectively assessed the information that is actually (and not hypothetically) communicated to families at this sensitive time, but it appears that most of the information provided is regarding the medical aspects of the condition, and usually does not focus on the social aspects of living with disability. Information also often follows the parents "lead," responding to questions that parents ask, rather than trying to present a minimally biased summary of the social and medical aspects of a particular condition (Skotko, 2005a,b; Munger, Gill, Ormond, & Kirschner, 2007; Gill et al., 2007).

The Decision to Continue the Pregnancy

For parents who choose to continue a pregnancy following an abnormal result, they are able to both prepare for the medical aspects of delivery and any subsequent medical treatment that may be required. Often this involves visiting medical specialists and delivering at a tertiary care hospital, and in some cases it may involve arranging for a special needs adoption. Some parents express frustration at the remaining uncertainties surrounding their future child's prognosis – often referred to as the concept of "knowing but not knowing" (Rempel, Cender, Lynam, Sandor, & Farquharson, 2004). Others report that the future child and his or her personality and interests remain abstract, yet the child's condition can seem concrete given the myriad of books, articles and specialists one can consult. The condition, therefore, can seem overwhelming and make it difficult to continue bonding with the unborn child. However, many parents also report that this time throughout the remainder of the pregnancy allows them to anticipatorily grieve their dream for a "healthy child," and to become excited about the birth of their future child, rather than undergoing the shock and anxiety that can come at the delivery of a newborn who is newly diagnosed. Some parents also report feeling more positively about the physical process of pregnancy and delivery (Ralston, Wertz, Chelmow, Craigo, & Bianchi, 2001).

The Decision to Terminate the Pregnancy

Parents who chose to terminate a pregnancy affected with a condition diagnosed prenatally are usually ending a wanted pregnancy, which can result in prolonged grief for some couples. Parents often respond to this emotionally difficult decision by wanting to move as quickly through the process as possible, selecting the termination procedure that seems most medical (e.g., a surgical abortion, rather than induction and delivery of the fetus). This can be further complicated if the parents do not have the opportunity to visualize the fetus through ultrasound and/or to obtain mementos such as a lock of hair, baby's footprint or photograph. For many expectant couples, the loss of their child is both the loss of the actual child and also the loss of the dreams for that hypothetical child (Seller, Barnes, Ross, Barby, & Cowmeadow, 1993). Leon (1995) writes: "Is pregnancy termination after fetal anomaly experienced as the death of a real damaged baby, the demise of the wished-for child, the disappointment of a thwarted pregnancy, the delay in one's dreams for parenthood, or a mark of self-deficiency ... More often than not this loss is multiple, a combination of the above factors."

Support is directly related to how individuals and couples cope with the grief associated with pregnancy termination after prenatal diagnosis (Leon, 1995). Professionals can assist families in coping with the emotional ramifications of pregnancy termination by making them aware of the various options for creating memories of their baby, even if they are saved at the hospital for a future time that parents request them. Some couples may be anxious about the societal implications of telling their friends and family, or even religious leader, about what has happened and about their decision to terminate the pregnancy. Helping these couples strategize ways to approach such difficult issues in advance can be useful. Although some researchers hypothesized that the more "active" role of pregnancy termination following prenatal diagnosis would intensify the psychosocial sequelae (Kolker & Burke, 1993), long-term responses appear similar to those noted in women dealing with perinatal loss for other reasons (Salvesen, Oyen, Schmidt, Malt, & Eik-Nes, 1997), and responses are more related to the severity of the condition than to the time of diagnosis during the pregnancy (Evans et al., 1996).

PROFESSIONAL ISSUES FOR FUTURE CONSIDERATION

Prenatal screening and diagnostic testing have been available for almost 40 years, and the list of conditions for which such testing is available will continue to increase. Already we are seeing the research availability of screening for a wide range of conditions through whole genome screening technologies such as CGH (Sahoo et al., 2006). The volume of information such tests can provide in a prenatal setting is combined with the challenge of having poor predictive ability for variants that have not previously, or have rarely been noted

(Manning & Hudgins, 2007). Additionally, prenatal testing is increasingly moving toward noninvasive methods that provide increasingly high sensitivity and specificity, and which may become diagnostic (e.g., maternal serum testing for free fetal DNA) in the next decade (Fan, Blumenfeld, Chitkara, Hudgins, & Quake, 2008). Given the observation that informed consent processes are held to a lower standard for non-invasive procedures, there is some concern that this may lead to couples giving less consideration to whether they truly want to undergo testing and obtain this information. This may lead to decisional conflict, decisions inconsistent with personal values, and potentially even social pressure to terminate newly diagnosed pregnancies affected with aneuploidy.

These two factors, the increasing availability of the number of conditions for which testing is available and the increasing non-invasiveness of such testing, will make prenatal genetic counseling and informed decision making by parents increasingly challenging. Health-care services will continue to face the contradiction between having shorter visit times and more quantity and complexity of information to convey to patients, particularly as awareness grows regarding the importance of personal values in such decision-making pre- and post-prenatal diagnosis. There is also, at least currently, a dearth of qualified health-care professionals to perform procedures and services, including genetic counseling, and to interpret test results, especially in more rural areas. Genetic and obstetrical care providers will need to find ways to effectively assess parents informational needs and personal values, and develop methods, such as computer based technologies, that can provide information in a personalized manner while addressing the relevant medical and social context of the conditions for which testing is being offered. Little research exists in these areas, and it is a critical component in providing evidence-based medicine.

CONCLUSIONS

Prenatal screening and diagnostic testing add a layer of complexity to the already emotional aspects of pregnancy and childbearing. Individuals providing prenatal genetic testing, screening, and counseling services should be aware of the psychological implications on parents and strive to acknowledge them in the counseling process, both before testing decisions are made and after a prenatal diagnosis is made. As testing becomes broader in its approach and less invasive while still maintaining high sensitivity, the potential exists for more and more couples to enter the prenatal testing process. As these changes occur, women and couples should consistently receive relevant information about their options for prenatal testing in a nondirective manner and should be encouraged to consider their options in terms of personal experiences and values.

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10

Single Gene Disease Risk

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INTRODUCTION

The diagnosis of a child with a single gene disorder can take on different meanings for different families. It is not uncommon for some families to arrive at a pediatric genetics clinic after months or years of searching for an underlying reason for their child's symptoms. The fact that, through genetic testing, clinicians can put a name to the collection of differences already noted in the child provides the family access to prognostic information, supportive resources, more accurate reproductive risk counseling, and possible relief from the burden of uncertainty.

After a diagnosis is reached, families often face many challenges in the adaptational process. It can be argued that, in some ways, these challenges parallel those of families who have a child with other chronic illnesses. Patients and their families may struggle with concerns related to treatment (or lack thereof), marital and financial strain, reallocation of family resources (both emotional and material), and access to medical and support care.

On the other hand, certain aspects of diagnosing a child with a single gene disorder represent a unique experience. The fact that a diagnosis is "genetic" elicits challenges for each member of the family. Although the idea of "genetic exceptionalism," that genetic information is qualitatively different from other health information, has been debated, this concept has generally been raised within the context of pre-symptomatic testing for adult-onset conditions and surrounds issues such as privacy and genetic nondiscrimination (Green & Botkin, 2003; Suter, 2001). The debate does not include the question of whether or not a genetic diagnosis poses a unique set of psychological risks to an individual or a family. There is evidence to suggest that this might be the case and includes parental guilt over passing on a "faulty" gene, altered self-concept among family members, impact on reproductive decision making, and family conflict surrounding the disclosure and communication of genetic information.

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In this chapter we will review the psychological implications of genetic testing for single gene disorders, highlighting similarities to and differences with other chronic illnesses and ways in which the genetic nature of an illness affects adaptation among patients and their families. Further, in light of the emphasis among clinicians and the public for early diagnosis and treatment, we will explore the diagnosis of single gene disorders through newborn screening. Due to the timing of newborn screening, diagnosis of single gene disorders generally precedes the onset of symptoms. This distinguishes newborn screening from traditional pediatric genetic testing and raises a distinct set of concerns for patients, their families, and the health-care system.

It is important in our discussion of the psychosocial implications of genetic testing to note that, unlike most areas of medicine, the field of pediatric genetics is relatively new. For example, few physicians were involved in human genetics prior to the 1950s. Before that time, genetics was largely the purview of Ph.D. research scientists. The 1960s and 1970s marked a turning point, with advances in knowledge of childhood genetic disorders and increased interest among pediatricians. As of 2003, there were an estimated 1,525 professionally active, board-certified medical geneticists in the United States (Cooksey, Forte, Benkendorf, & Blitzer, 2005). Much of the burden for diagnosis and management of single gene disorders currently lies with medical geneticists and other genetics professionals; however, this is likely to change in the future as the number of recognized syndromes and defined molecular tests increases and the demand for genetic services outstrips the supply of qualified genetics professionals in the United States and elsewhere. The challenges this will present for future families are likely to be numerous and yet unrealized, and may include the potential for under-informed health-care providers and potentially missed opportunities for psychosocial and medical interventions in at-risk families.

The ability to test for single gene disorders has a similarly short history. This is best highlighted by two historical milestones: (1) identification of the structure of DNA in 1953 and (2) completed sequencing of the human genome in 2003. To say our knowledge of the clinical implications of testing for single gene disorders has grown exponentially in the intervening 50 years is an understatement. Identifying the genes responsible for disorders such as cystic fibrosis (CF), Duchenne muscular dystrophy (DMD), and sickle cell disease has dramatically increased our understanding of these conditions and led to earlier diagnosis, allowing for improved management and greater reproductive options for families. Importantly, knowledge of the molecular and genetic basis of single gene disorders has, in some cases, also elucidated the natural history of these disorders and led to elimination and/or prevention of many associated complications.

And yet, knowledge of the psychosocial implications of performing genetic testing for single gene disorders lags behind. Much of what is known is based on research involving a limited number of conditions, for example, CF and DMD. More research is needed to explore the effects of genetic testing on other single gene disorders with a broader spectrum of

disability. However, there are lessons to be learned about what it means to receive a diagnosis of a single gene disorder from this subset of conditions. This information is reviewed below.

PATIENT ADAPTATION

Through research studies and clinical experience, it has become clear that the experiences of individuals diagnosed with a single gene disorder are variable and depend, in part, upon the nature of the condition. The obstacles of a child who is diagnosed with a condition featuring profound mental retardation and/or physical abnormalities will likely be different than those of a child who is diagnosed with a condition featuring normal cognitive abilities and few visible manifestations. That being said, similarities across conditions can be drawn. Studies seeking to understand what it means to be diagnosed with a genetic condition in childhood have tended to focus on parent report, retrospective adult narratives, or quality-of-life measures. This is due, in part, to the difficulty in assessing adaptation among young children who might not be able to reflect upon their own illness-related experiences. It is also the case that many children are not fully informed of the genetic nature of their diagnosis until adolescence and, therefore, might not incorporate the condition into their self-identity until years after the diagnosis is made. Although these issues generate limitations in our ability to capture the experience of being diagnosed with a single gene disorder, several important themes have emerged.

As with other chronic childhood illnesses, children diagnosed with a single gene disorder can experience feelings of social isolation (Nadeau & Tessier, 2006). This is reiterated both among parents of children with cystic fibrosis, an autosomal recessive genetic disorder featuring chronic lung infection and malabsorption leading to poor growth, who report that their children feel different from their peers and are teased more often at school, and among adults with various single gene disorders who indicated feelings of social isolation throughout life (Beadle, 2004; Foster, Bryon, & Eiser, 1998; Petersen, 2006). It is unclear from the literature whether or not this sense of social isolation is secondary to the genetic nature of the illness or more basic elements of the illness itself, such as frequent absence from school or reduced participation in normal childhood activities due to medical or physical limitations.

Regardless of the underlying etiology, the presence of social isolation among children diagnosed with a genetic disorder is important to address and presents an area for possible intervention. The emergence of disease-specific summer camps is among the ways to address feelings of social isolation. This is an increasingly available option for children with single gene disorders, including neurofibromatosis, a neurological condition that involves the growth of often disfiguring benign tumors along nerve roots and multiple large brown birthmarks, and Duchenne muscular dystrophy (DMD), a progressive neuromuscular disease resulting in muscle wasting and weakness.

Disease-specific summer camps are often directed toward a subset of children who have limited access to normal childhood activities or who might feel isolated from other children. Summer camps can serve a vital role in helping children adapt to the diagnosis of a genetic disorder by normalizing their experience and connecting them with a group of similarly affected peers. They also provide a safe venue for children to ask questions about the genetics of the condition and future implications (e.g., reproductive options).

Children who are diagnosed with a genetic condition may experience adversity throughout life; however, successful adaptation and adjustment is possible. Recent studies of children with DMD and CF have revealed many to be functioning well and healthy adjusted individuals (Szyndler, Towns, van Asperen, & McKay, 2005; Nereo & Hinton, 2003). In fact, Szyndler et al. (2005) reported lower rates of mental health problems among adolescents with CF compared to their physically well peers. These findings, contrasting previous studies suggesting higher rates of psychosocial disruption among children with CF, were attributed to better treatment and prognosis in recent years (Boyle, di Sant'Agnese, Sack, Millican, & Kulczycki, 1976; Szyndler et al., 2005).

Many factors appear to play a role in successful adaptation. These include family support, hope and optimism for the future, and normalization. Aspects of family functioning, including cohesion and supportive behaviors, have been associated with coping, adjustment, and adaptation among children with CF (Levers & Drotar, 1996; Graetz, Shute, & Sawyer, 2000). The purported effects of family support have widened to include actual health outcomes, such as improved eating behavior and increased energy level (Szyndler et al., 2005). Recent studies have explored the association between hope for the future and patient adaptation and found that greater hope for the future was correlated with lower rates of psychosocial disruption among adolescents with CF (Szyndler et al., 2005). What is of equal interest is that degree of hope and optimism was independent of disease severity, suggesting a benefit from maintaining a hopeful outlook, regardless of prognosis or disease characteristics.

Apart from maintaining a hopeful outlook, individuals often seek to normalize their experience (Petersen, 2006). The process of normalization, whereby an individual's thoughts and behaviors are made to seem normal, is similar to individuals with other nongenetic chronic illnesses, who use this strategy as a way to adapt to the diagnosis and maintain a daily regimen (Charmaz, 2000).

One important aspect of a single gene disorder is its implication for future generations. Individuals affected with an autosomal dominant single gene disorder (change in one copy of the gene) face a 50% chance with each pregnancy for having an affected child. If the specific genetic mutation responsible for the disorder has been identified, then prenatal diagnosis is possible. What is not possible, however, is predicting the degree of disease severity in any given individual who inherits the mutation. Autosomal dominant disorders are often extremely variable. This means, for example, that a parent with a relatively mild presentation of neurofibromatosis could have a child who has disfiguring/life-threatening

tumors or skeletal manifestations that would significantly impair quality of life.

With the availability of prenatal testing, individuals have increasing options surrounding prenatal testing and screening. The fact that an individual faces these choices differentiates single gene disorders from other nongenetic chronic illnesses. Individuals with a variety of single gene disorders report confronting issues related to reproductive decision making (Petersen, 2006). They worry not only about their own health and ability to be a reliable parent but also about the future health status of the unborn child (Petersen, 2006). Greater exploration of the reproductive decision-making process is warranted, as we still have limited understanding of how affected individuals make decisions about prenatal testing and the decision to start a family.

PARENT AND FAMILY ADAPTATION

Diagnosing a child with a single gene disorder can have significant and long-lasting implications for the parents and family. Simply performing genetic testing may be stressful for parents and can result in increased depression and anxiety symptoms, regardless of test result (Pilnick & Dingwall, 2001). If the result is positive and a child is diagnosed with a genetic condition, parents struggle to adapt to the new diagnosis and make meaning of the illness within the family. Such challenges, including increased family stress, financial strain, and caregiver burden, are not unique to single gene disorders and have been reported among families with nongenetic chronic health conditions (Wang & Barnard, 2004).

Once the initial crisis subsides, families attempt to attain a level of normalcy. The ability of a family to successfully function post-diagnosis appears related more to family characteristics and level of support than aspects of the disease itself or the child's level of disability (Chen & Clark, 2007). Families who experience greater distress and lower emotional support are at risk for poor psychological adjustment, while families with increased "hardiness," defined as the presence of internal strength and resilience, have better family functioning (Chen & Clark, 2007; Szyndler et al., 2005).

Lewis and Khaw (1982) applied Olson's circumplex model of family functioning to the adaptation process of families who have a child with CF. The premise of this model is that families must balance cohesion and adaptability, allowing for change throughout the life cycle, in order to successfully cope with stress (Olson, Sprenkle, & Russell, 1979). Lewis and Khaw suggested that CF families exhibit increased adaptability and cohesion following diagnosis and during periods of illness exacerbation, and return to a more stable state after the crisis subsides. Another theoretical approach applied in the literature is the resiliency model of family stress, adjustment, and adaptation (McCubbin & McCubbin, 1993). This model incorporates two phases: adjustment and adaptation. During the adjustment phase, families strive to manage the immediate stressor without lasting change to family functioning. The adaptation phase is defined

as the attempt to bring about a long-term balance and cohesion within the family that allows for successful coping on an ongoing basis. Incorporating theoretical models into research on family functioning allows for a broad approach to families of children diagnosed with a single gene disorder. The specific stressors often vary between conditions; however, family support and internal family resources may have a greater role in adaptation than level of disability. Once at-risk families are identified, interventions that increase support and draw upon existing family strengths can be applied, regardless of the condition. Possible interventions include genetic counseling, support groups, couples therapy, and information and education, although the efficacy of such interventions deserves thorough exploration (Dine & Terzioglu, 2005; Foster, Bryon, & Eiser, 1997; Beale, 2006).

Psychological Implications for Mothers

The psychological implications of diagnosing a child with a single gene disorder have been explored more often with mothers than fathers; however, there is reason to believe that mothers experience more significant distress than fathers and that this distress directly or indirectly impacts the health and well-being of the affected child (Patterson, McCubbin, & Warwick, 1990). Mothers of a child with CF can feel stress related to disseminating genetic information within the family, the responsibility for care of the affected child, and coping with an altered identity (Hodgkinson & Lester, 2002). Unlike other chronic health conditions, mothers of a child with a single gene disorder describe feelings of guilt related to their carrier status and subsequent changes in self-image (Hodgkinson & Lester, 2002). Studies suggest that how well mothers cope with their child's diagnosis is unrelated to the age of the child or clinical factors associated with the condition, and may be more strongly related to psychosocial factors, such as support and family functioning (Foster et al., 1997).

Similar to their affected children, mothers appear to be at risk for social isolation and can benefit from encouragement from health-care providers. They use strategies such as downward comparison, comparing their experience to those with more serious health problems (i.e., pediatric cancer), to normalize their child's experience and maintain a positive attitude about the condition (Gallo, Angst, & Hadley, 2005). And, as with their children, hope and optimism about the future are important factors in the adaptation process and have been associated with higher quality of life and greater success at keeping the child healthy (Bailey, Sideris, Roberts, & Hatton, 2008; Hodgkinson & Lester, 2002). Such findings suggest that interventions to increase support and optimism could play an important role in successful adaptation among mothers, as well as their affected children.

Impact on Reproductive Decision Making

There are at least two main areas in which adaptation to a single gene disorder contrasts with the diagnosis of other chronic illnesses:

the potential implications for other family members and the impact on reproductive decision making. When a child is diagnosed with a single gene disorder, the at-risk status for other family members may be revealed. This can include other biological children in the same family, cousins, aunts, or uncles. While they may not be at risk for developing the condition themselves, in the case of recessive disorders, they can be carriers of the gene mutation. Knowledge of carrier status is deemed important by health-care providers due to the impact on future reproductive decisions. For this reason, dissemination (family communication and disclosure) of the genetic nature of the condition is generally encouraged. Parents, specifically mothers, have reported feeling "in the middle" after their child is diagnosed (Hodgkinson & Lester, 2002). While some family members welcome information about the genetic condition and pursue carrier testing, others harbor more negative feelings. Mothers have reported family disunity following the diagnosis of a single gene disorder in the family and sense blame among family members for causing the illness to occur, regardless of their lack of control over the child's diagnosis (Hodgkinson & Lester, 2002). Parents may feel they are the bearers of "bad news" in the family and experience increased stress surrounding the condition. Increased stress surrounding the genetic nature of the condition and negative reactions from extended family members can decrease family emotional support, create conflict within the family, and impair adaptation.

In addition, parents worry about the genetic status of current or future children. Clinically, parents often focus on the health of older siblings and may perceive that their normal childhood illnesses are manifestations of the disease. Even after older children are determined to be unaffected, parents may still worry excessively about carrier status and pressure health-care providers to perform genetic testing on young children. Genetic testing of asymptomatic siblings is discouraged for several reasons, including value placed on informed consent, and reflects the American College of Medical Genetics-supported position statement on genetic testing in minors (1995). This policy places some parents in conflict with health-care providers and may result in frustration for both parties involved.

Parents who desire additional children are faced with tender decisions regarding prenatal testing and the potential for having another affected child. Prenatal testing raises many complicated issues, not the least of which surrounds the "value" of the affected child within the family. The availability of prenatal testing surrounding single gene disorders is unique to the genetic nature of the illness and is addressed elsewhere in this volume.

IMPLICATIONS OF DELAYED DIAGNOSIS

The process of obtaining a diagnosis for a single gene disorder generally involves identification of physical or developmental differences followed by multiple medical appointments over months to years, as

evidenced by the experience of families of a child diagnosed with fragile X syndrome (FXS). FXS is the most common inherited cause of mental retardation with an incidence of 16–25/100,000 males and approximately one-half that for symptomatic females (Saul & Tarleton, 2008). It is not detectable through physical or behavioral evaluation in the newborn period. Although there is a well-recognized phenotype, the first sign that a child has FXS is usually developmental delay. According to a survey of over 450 families with an affected child, the average age of first concern was 15.6 months (Bailey, Skinner, & Sparkman, 2003). In contrast, the average age at diagnosis was 60 months. Most families described themselves as being the first to identify concerns with their child's development and commonly are advised to "wait and see" by a health-care provider. Parents voiced difficulties convincing a health-care provider that something was not quite right with their child and had to visit a number of health-care professionals in order to obtain a proper diagnosis. On average, early intervention services were not obtained until the child was 2 years of age – which is 9 months beyond the initial identification of concerns by most parents. In addition, 55% of parents had another child while searching for the diagnosis. Not surprisingly, parents of children with FXS and health-care providers have expressed support for early diagnosis through newborn screening with 60% of parents indicating that they did not believe a diagnosis of FXS in the newborn period would disrupt bonding (Skinner, Sparkman, & Bailey, 2003).

The diagnosis of a child with an inborn error of metabolism can be an arduous process, unfamiliar to most families and their primary care physicians. Alternatively, a child can experience an acute decompensation in the first few weeks of life and die from an unrecognized metabolic crisis. Presenting symptoms (e.g., developmental delay, vomiting, and lethargy) are nonspecific and associated with a number of genetic and nongenetic etiologies. In the former case, it is not uncommon for a family to wait months to years between initial concerns and a confirmed diagnosis. On this diagnostic odyssey, the family may interface with a number of health-care professionals, developmental and other medical specialists, clinical geneticists, and genetic counselors. This is both a frustrating and time-consuming process. In the latter case, an infant dies without a confirmed diagnosis and the increased recurrence risk for subsequent offspring goes unrecognized.

Beyond the medical benefit of early diagnosis, studies have shown associations among age of diagnosis, adaptation, and family functioning (Chen & Clark, 2007). Earlier diagnosis has been associated with better family functioning and adaptation compared with families who received a later diagnosis (Chen & Clark, 2007). Possible explanations include early access to medical care and support systems, increasing time to adapt to the diagnosis, and avoidance of the "diagnostic odyssey" referred to previously. Timing might also influence family opinions of the diagnostic period. A study from the Netherlands comparing the experiences of families whose child was diagnosed with CF early (<3 months) vs. late (>3 months) found that significantly fewer parents in the early diagnosis group described the pre-diagnostic period negatively (Merelle et al., 2003).

In utero diagnosis allows families the most time to prepare for the birth of child with a genetic disorder; however, this is impractical for most conditions, given lack of awareness about carrier status, procedure-associated risk with prenatal testing, limited access to prenatal care, and ethical issues surrounding population-based prenatal testing programs for single gene disorders. An economically feasible and rapidly expanding alternative is newborn screening, which allows for diagnosis of a single gene disorder in the immediate neonatal period. Through newborn screening, it is now possible to perform population-wide screening for many single gene disorders either based on common mutations in the population or by testing for abnormal metabolites in blood. In this section we will discuss some of the more pressing psychosocial and medical implications of newborn screening for children and their families.

NEWBORN SCREENING

Much can be learned about the current excitement and controversy surrounding newborn screening (NBS) by briefly reviewing its historical context. The advent of NBS began in the early 1960s with Robert Guthrie's discovery that newborn blood, transferred to a piece of filter paper, dried, and transported to a laboratory, could reliably screen newborns for phenylketonuria (PKU), an autosomal recessive disorder producing profound mental retardation if not treated with a phenylalanine-restricted diet beginning in the first 3–4 weeks of life. Early identification and lifelong treatment of the disorder with a phenylalanine-restricted diet prevents the profound mental retardation seen universally in untreated individuals.

While most acknowledged the early success of NBS in preventing the devastating consequences associated with untreated PKU, support was not universal. As is true in many areas of genetics, technology far outpaced knowledge about treatment, natural history of the condition, and psychosocial implications for affected individuals and their families. Standardized treatment protocols were not in place at the initiation of NBS for PKU. It was unclear whether or not to treat individuals with variant forms of PKU and how long individuals should remain on the restricted diet. As a result, there were a number of negative consequences, including treatment of unaffected individuals and inadequate dietary restrictions for at-risk individuals. Regardless, the benefit of early detection in the prevention of significant disability was compelling and support for NBS quickly spread throughout the United States, later expanding to include other single gene disorders.

Recently, advances in newborn screening technology have improved the ability to diagnose single gene disorders with greater sensitivity and specificity. The majority of conditions screened through this "expanded" NBS are autosomal recessive, single gene disorders involved in the metabolism of proteins, fats, or carbohydrates including organic acidemias, aminoacidopathies, and fatty acid oxidation disorders. Most affected infants are born to families with no known family history of the

disorder. Currently, all 50 states and the District of Columbia have individual laws surrounding newborn screening; no national policy exists. Although each condition is, by itself, rare, screening for >20 disorders has been estimated to identify ~1 case per 2,400 births. At 4 million births in the United States per year, one would expect ~1,600 affected newborns. Given the widespread support for expanding newborn screening from the general public and many segments of the public health community, and a growing list of disorders amenable to NBS, this number will continue to increase in the future.

The process of newborn screening is relatively straightforward. A small sample of blood is obtained from the newborn through a "heel stick" in the birth hospital prior to discharge, generally 24–48 h after delivery. The sample is tested and categorized as either "screen negative" or "presumptive positive" for each disorder in the panel. As the name indicates, these are screening tests with cutoff values set so as not to miss any true-positive individuals. As a result, approximately seven in eight infants detected as "presumptive positive" will be found *not* to have the condition in question following definitive testing.

Results are communicated to the family in a variety of ways, ranging from direct contact from the state health department to a phone call from the child's pediatrician. Rapid follow-up and confirmation of abnormal results is crucial to the success of the NBS program in reducing morbidity and mortality for affected infants and in preventing infants who are false positive from being treated unnecessarily and is best facilitated through the child's medical home. The concept of a medical home was introduced in an American Academy of Pediatrics Policy Statement (1992) and later expanded to describe a model for delivering continuous, accessible, comprehensive, compassionate, coordinated, culturally sensitive, and family-centered care (American Academy of Pediatrics, 2002). Unfortunately, only 24% of states have a procedure for making sure that screen-positive infants have a medical home (Kim, Lloyd-Puryear, & Tonniges, 2003). Without this in place, the ability of state NBS programs to accurately diagnose and manage infants with potentially life-threatening genetic conditions is much more difficult. In fact, clinical follow-up has been identified as the single largest challenge for state NBS programs (James & Levy, 2006).

How and when families are informed regarding the results of NBS and the potential implications of an abnormal result has been hotly debated. In contrast to recommendations from the American Academy of Pediatrics Task Force (2000), most mothers are provided with educational materials on the disorders to be screened while in the birth hospital, generally immediately prior to the consenting process, if required, and sample collection (Kim et al., 2003). Despite recommendations from the National Work Group on Literacy and Health that all health literature be written at or below a 6th grade reading level, a recent study revealed an average readability of NBS materials at the 10th grade level (Fant, Clark, & Kemper, 2005).

Written informed consent is generally not required by law; therefore, families who face abnormal results are under-informed and ill-equipped

to cope with this information. This raises concerns for children and their families who might be among those affected with a genetic disorder ("true positives") and influences their ability to adequately process and adapt to the new diagnosis.

Studies on the impact of NBS on children and their families can be divided into four main areas: (1) medical and developmental outcome for the child; (2) psychosocial implications for the parents; (3) psychosocial implications for the child; and (4) impact on future reproductive decision making for parents, children, and extended family members. Each area is reviewed below.

Medical and Developmental Outcome for the Child

The positive impact of early detection by NBS on patient outcomes has been well documented. A recent study compared the expected number of children with mental retardation (based upon disease incidence) with observed numbers. Data was obtained by linking newborn screening records with special education and developmental disability databases (Van Naarden Braun et al., 2003). Although limitations in this method are acknowledged, the authors reported a lower-than-expected frequency of developmental disabilities secondary to metabolic or endocrine disorders. This was presented as evidence for the effectiveness of newborn screening in a given region.

Others have compared the clinical outcome of children with metabolic or endocrine disorders identified from clinical symptoms with that identified through newborn screening. Infants identified through newborn screening had less need for intensive care prior to diagnosis, earlier initiation of treatment, a decreased number of hospital admissions, and a reduction in the number of days per hospital admission (Waisbren et al., 2003).

The impact of newborn screening on developmental outcome of children with genetic disorders has also been well documented. Infants identified through newborn screening had a higher developmental quotient than those identified by the onset of clinical symptoms (Waisbren et al., 2003). In the study by Waisbern et al. (2003), almost half of the children diagnosed with an inborn error of metabolism (associated with cognitive delay when untreated) outside of newborn screening had significant deficits in communication, motor and social skills, and daily living skills, whereas none of the children identified through newborn screening had similar problems. Another study by Weber, Scholl, and Baumgartner (2004) reported similar encouraging results among children diagnosed with biotinidase deficiency, a rare metabolic disorder requiring early biotin supplementation. The study found no cases of hearing or vision loss (common in untreated biotinidase deficiency), and motor and speech skills were comparable to those of their peers. Although the study involved a small number of affected individuals, it does provide support for the positive developmental impact of newborn screening among infants with potentially treatable genetic disorders.

In contrast to the positive implications of NBS in identifying affected individuals, studies since the inception of NBS have suggested a possible impact of false-positive results on child's health outcomes. Researchers in the late 1960s identified a typical response among parents of children with false-positive NBS results, termed the PKU anxiety syndrome (Rothenberg & Sills, 1968). The "syndrome" is characterized by acute or chronic anxiety, worry about child's health status, and uncertainty about test results. Although initially noted with PKU screening, this has been extended to encompass other NBS conditions (Rothenberg & Sills, 1968; Tluczek et al., 1991, 1992). Outside of NBS, the chronic parental anxiety about an otherwise healthy child has been documented. The "vulnerable child syndrome" was first described by Green and Solnit (1964). They discovered that children who recovered from a near-death experience in early childhood were incorrectly seen by parents to be at increased risk for later illness or accident, leading to overprotection and subsequent child behavior problems. Within the context of NBS, researchers have cited this as a possible explanation for increased maternal worry about their child's future and increased number of hospitalizations during early childhood among false positives compared with a normal-screened group (Gurian, Kinnamon, Henry, & Waisbren, 2006; Waisbren et al., 2003). Interestingly, this phenomenon was not noted among families who were referred to a metabolic center.

Increased hospitalizations and worry about child's health status could not only affect downstream health-care costs but also result in long-term implications for the child. Research on families with a positive NBS for congenital hypothyroidism found that 50% of children with false-positive results continued to show disturbed behavior 4 years after receiving a normal repeat screen (Fyro & Bodegard, 1987). In addition, increased maternal stress in early infancy has been associated with elevated cortisol levels in the child and greater mental health symptoms (Essex, Klein, Cho, & Kalin, 2002). Taken together, this raises significant concerns about possible iatrogenic effects of NBS on the thousands of children with false-positive results.

The theory behind potential iatrogenic effects of NBS can be further explained by the "nocebo" phenomenon, described by Kennedy (1961). A review by Robert Hahn (1997) defines the nocebo effect as "the causation of sickness (or death) by expectations of sickness (or death) and by associated emotional states" (p. 607). Two forms are described: specific and general. In the former, a person expects one negative outcome with consequent realization of that expectation. This is less applicable for NBS; simply thinking that a child has a metabolic disorder will not cause that to be true. However, the *general* nocebo effect does have important public health implications in that negative expectation causes unspecified adverse health outcomes (e.g., sickness). The ability of negative suggestion to produce negative health outcomes has long been demonstrated by social psychologists. It has only recently been applied within the context of NBS as a possible consequence of false-positive results (Gurian et al., 2006). Without adequate education about the process of newborn screening and the meaning of "presumptive positive" results, state programs could

generate increased parental anxiety leading to actual adverse health outcomes in otherwise healthy newborns.

Clinically, mothers of children with presumptive positive results, who are later determined to be unaffected, often continue to worry about their child's health status. For example, mothers of infants who are presumptive positive for galactosemia (a metabolic condition characterized by lack of a liver enzyme needed to digest galactose, found in milk products) often discontinue breastfeeding, long after reassurance by health-care providers of the child's unaffected status. Breastfeeding has been associated with long-term benefits for newborns, including decreased obesity rates and lower risk for type II diabetes (http://www.cdc.gov/breastfeeding/). In addition, breastfeeding is an important source of maternal–infant bonding and has been associated with reduced risk for breast and ovarian cancer among women (Ip et al., 2007). The downstream health effects of withholding this nutritional source from a population of otherwise healthy infants are not known, but potentially significant.

Psychosocial Implications for Family

The birth of a child can be a stressful time for any family. Parents face the physical strain of childbirth, emotional toll of entering into a new parenting relationship, and the financial costs of a growing family. This results in a fragile state, even under the best circumstances. Adding NBS into the mix threatens the delicate balance parents maintain between joy over the birth of their child and normal parental fears and anxieties. When an abnormal NBS is identified, it is not immediately clear whether or not the child will be a true or a false positive. Often there are no physical signs or clinical symptoms to predict outcome, leading families to wait days to weeks with the thought of their newborn having a potentially life-threatening genetic condition. Given the fact that most conditions are rare and unfamiliar within the general population, this creates an emotional roller coaster for the family marked by disbelief, confusion, and fear. On the other hand, as previously outlined, early diagnosis through NBS can have many benefits for the family including early access to medical and support systems, better family functioning, and adaptation to the diagnosis. What is less clear is whether or not the benefits for affected children and their families outweigh the risks for those parents whose child receives a "false-positive" result.

False positives present a significant challenge to any screening program, and newborn screening is no different. As described earlier, the term refers to an initially out-of-range result, followed by normal result on subsequent definitive testing. Initially abnormal levels can be due to transient factors, a variant and less severe form of the disorder, or (in some cases) carrier status of the disorder. It is usually not the result of laboratory error. Depending upon the case, an abnormal result necessitates repeat screening or confirmatory testing prior to establishing a diagnosis. The urgency of repeat screening is somewhat dependent on other factors, including the age of the child, the presence or absence of symptoms, and the "degree" of abnormal result (borderline vs. grossly elevated). Similar to

prenatal maternal serum screening, the goal of newborn screening is to maximize the identification of affected individuals, while holding the number of false positives to an acceptable level. This "acceptable level" varies by condition and state NBS program. It has been estimated that approximately 1 in 300 infants receives a false-positive result, roughly equating to 13,000 infants/year in the United States alone, or a false-positive to true-positive test ratio of 8:1 (Center for Disease Control and Prevention, 2003). This is a staggering number to consider, given the rapid expansion of NBS within the past 40 years and the push to further expand state programs to include additional disorders. Unfortunately, most literature provided to families on NBS does not stress the possibility of a false-positive result. Among 46 states surveyed, only 6 (13%) mentioned the possibility of a false-positive result on NBS materials provided to parents (Fant et al., 2005). The implications of false-positive results for the family cannot be ignored and include disrupted parent–infant bonding, increased parental stress, and altered perception of child's health status.

For many families, bonding occurs and/or is significantly strengthened shortly after delivery. Clinical experience and research within the field of nursing has shown that adverse events in the neonatal period can alter and/or disrupt the normal bonding process. Grief over loss of the "normal" baby and concern about an infant not surviving the neonatal period can result in delayed attachment and bonding (Kenner, 2003). Neonatal intensive care (NICU) nurses are trained to recognize signs of altered parent–infant bonding, such as not touching or holding the baby, and intervene accordingly (Franklin, 2006; Kenner, 2003). Given that most babies with abnormal NBS results are not yet symptomatic, this raises the question: does the *possibility* of future illness elicit a similar parental response?

Shock, anger, fear, blame, confusion, sadness, depression, loneliness, shame, and frustration are among the feelings expressed by parents whose newborns failed a hearing screen (mandatory part of the NBS process in 38 states and District of Colombia) (Yoshinaga-Itano & Abdala de DeUzcategui, 2001). Such strong emotions experienced within the first weeks after delivery have the potential to affect early parent–child bonding. This is a difficult and somewhat poorly defined concept to measure. Instead, a number of research studies have used standardized measures to examine parental stress following an abnormal NBS result. Increased parental stress can alter the ability to attend to the child's needs, consequently disrupting early parent–child relationships (Tluczek et al., 1991, 1992). Pipp-Siegel, Sedey, and Yoshinaga-Itano (2001) measured parental stress at 6-month intervals among parents of infants with hearing loss. They found significantly higher scores on the Parental Distress subscale of the Parental Stress Index (PSI) among mothers of children with hearing loss compared with that of normally hearing children. However, they also noted that stress levels were lower among mothers whose children received intervention services and had greater language skills. Children identified with hearing loss through NBS often receive the benefit of early intervention services and have greater language skills than do their later-identified peers. This led the authors to conclude that early identification

did not lead to increased parental stress and subsequent problems with bonding when compared with a sample of later-identified children with hearing loss (Yoshinaga-Itano, 2003; Pipp-Siegel et al., 2001). Similarly, when comparing mothers of children diagnosed with biochemical genetic disorders through NBS, the vast majority of which are single gene disorders, with mothers of a group of children identified by clinical symptoms, Waisbren et al. (2003) found lower levels of parental stress among the NBS group. Further exploration revealed an association between maternal stress and knowledge about NBS, with greater knowledge correlating with lower stress. Interestingly, no difference was noted between fathers of children from the NBS vs. clinically identified group. While both studies indicated a decrease in stress among mothers of affected children identified through NBS, the comparison group was a clinically identified population and did not compare to a group receiving false-positive results.

Waisbren et al. (2003) attempted to address this question by specifically measuring parental stress in families with false-positive results. They found a significant increase in stress among mothers (again, not fathers) in the false-positive group compared with those who received normal NBS results. Factors associated with a decrease in stress included receiving results of the repeat NBS in person and referral to a metabolic specialist. This finding was replicated in a study comparing parents receiving a false-positive NBS result with parents in a normal-screened group, assessed at $\geq$6 months of age (Gurian et al., 2006). Mothers in the false-positive group had significantly higher scores on the Difficult Child and Parent–Child Dysfunction Interaction subscales of the PSI. No significant difference was identified between fathers in the two groups; however, only 46 fathers participated compared with 166 mothers. In a literature review by Hewlett and Waisbern (2006), eight of nine studies on parental response to newborn screening noted an association between parental anxiety and/or depression and need for repeat NBS, regardless of whether or not the repeat screen was normal. Additionally, differences in parent–child dysfunction were noted, which might reflect altered parent–infant bonding. How health-care providers respond to increased parental stress from abnormal NBS is often inadequate relative to families' needs. Although mothers clearly have increased stress surrounding abnormal NBS results, in one study only 50% recalled being told the result of the repeat screen with 22% indicating that they were told "no news is good news" (Gurian et al., 2006).

Psychosocial Implications for Patients

The important questions raised by NBS are: What are the long-term psychosocial implications for individuals diagnosed with a genetic disorder at birth? Does early diagnosis and "labeling" influence self-concept and quality of life among children and adolescents? How does the experience differ from individuals with other chronic health disorders (e.g., type 1 diabetes) or children who are diagnosed with a single gene disorder through more traditional means? Relatively few studies have attempted to answer

these questions, and results are conflicting with some reporting little difference in quality of life or psychological outcomes and others reporting significant behavioral differences.

Bosch et al. (2007) assessed course of life, health-related quality of life, and sociodemographic outcomes of 32 adults with PKU. Adults, aged 18–30 years, were compared to matched non-PKU adults. No significant differences were identified on quality-of-life scales, course of life questionnaire, or percentage employed. The only significant difference was the percentage who received special education during primary school, noted to be higher in patients with PKU. With the exception of reduced positive emotions, Landolt, Nuoffer, Steinmann, and Superti-Furga (2002) have reported normal adjustment and quality-of-life measures among individuals with PKU when compared to their siblings. The results, while encouraging, contrast with other studies reporting difficulties among adults with PKU in social life and psychosocial issues (Stemerdink et al., 2000; Hendrikx et al., 1994; Ris et al., 1997). Koscik et al. (2005) compared the quality of life of children diagnosed with CF through NBS with that of clinically identified children. Interestingly, the study found no difference in health-related quality of life among a sample of younger children (age 10 years and older). Limitations to that study included a total sample size of <40 participants and the absence of a CF-specific, validated quality-of-life measure.

Weglage et al. (2000) compared individuals with PKU or type I diabetes with healthy controls and found no difference in outcome measures (IQ, psychological profile, and externalizing problems) between those with PKU and those with diabetes, a chronic health condition that involves similar lifelong dietary restriction and management. However, both groups had significantly elevated internalizing problems (e.g., anxiety, depression, social isolation) compared to healthy controls. This suggests that the psychological consequences of a subset of single gene disorders (i.e., metabolic conditions) may mirror those of other chronic health conditions. This can provide health-care providers and researchers with a framework in which to explore emerging psychosocial issues for affected individuals diagnosed through NBS.

What is lacking from many of the studies on NBS is an exploration of self-concept among individuals diagnosed with a single gene disorder in childhood. One might argue, given the positive benefits of earlier diagnosis on family functioning and adaptation, that there would be a greater likelihood for positive self-concept and adjustment among individuals diagnosed through NBS, mediated by better family and social support. On the other hand, it is possible that being labeled with a genetic condition from birth fundamentally alters one's sense of self and negatively impacts interpersonal interactions and decision making. Future studies, employing more sensitive measures, are needed to better capture the experience of individuals diagnosed through NBS. Without this knowledge, we are largely uninformed about the psychological consequences of a population-wide program to identify single gene disorders in childhood.

Implications for Reproductive Decision Making

As previously mentioned, one notable distinction between other chronic health conditions, such as diabetes, and single gene disorders is the significance of genetic information for siblings and other at-risk family members. Most genetic disorders included on NBS panels are autosomal recessive, meaning parents of an affected infant are obligate carriers and have a 25% chance with each pregnancy for having another affected child. Parents who learn of their carrier status following the birth of an affected infant can then choose to pursue prenatal testing during any subsequent pregnancy. The potential impact on future reproductive decision making has been identified as a side benefit to NBS for genetic disorders, but not as a primary reason for inclusion (Botkin et al., 2006).

Future Challenges

The challenges illustrated by false-positive results represent only a fraction of those that could be raised herein. Recent technological advances have greatly expanded the number of conditions available for screening. Inclusion of some conditions is of clear benefit for patients and their families and fulfills traditional NBS criteria (Wilson & Jungner, 1968). For example, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a relatively common metabolic disorder (1 in 25,000), featuring the inability to break down medium-chain fats during periods of fasting or illness, resulting in episodes of severe hypoglycemia causing permanent brain injury, and is fatal in 30–50% of patients. Avoidance of fasting, particularly in young infants, and maintenance of normal blood glucose levels with oral or intravenous glucose during periods of illness largely prevent such deaths and greatly improve overall prognosis. The medical benefit of screening for and identifying infants with MCAD in the newborn period is without question.

For other conditions that respond less consistently to treatment, or conditions without available treatment, inclusion in the state NBS program is much less straightforward. Although some patients respond to early treatment and intervention, others experience devastating metabolic crises despite early detection and close monitoring. Is newborn screening for such conditions justified, given the lack of adequate treatment and potential false hopes raised for families? Since current NBS techniques involve screening simultaneously for a large number of metabolites, it is difficult to include some disorders while excluding others.

Under intense discussion has been the expansion of NBS to include lysosomal storage disorders (LSDs). Inclusion is of interest to many health-care providers and families as a result of the recent success of enzyme replacement therapy (ERT) in improving the length and quality of life among individuals with Gaucher, Fabry, and Pompe diseases or mucopolysaccharidosis I, II, or VI. Untreated, these disorders result in considerable morbidity and mortality. However, arguments surrounding LSD screening are not clear-cut. There are >40 LSDs with a combined incidence of 1 in 5,000 in the general population, and the majority of them

involve progressive central nervous system impairment that is not treated by ERT. Also, many disorders, such as Pompe disease, have both infantile and late-onset forms. According to epidemiological data, the estimated ratio of late-onset to infantile cases of Pompe disease identified through NBS is ≥2:1 (Kemper, Hwu, Lloyd-Puryear, & Kishnani, 2007). An Italian study on NBS for Fabry disease identified an 11 to 1 late-onset to classic infantile phenotype ratio (Spada et al., 2006). Individuals with the infantile form of Pompe disease or classic Fabry disease would greatly benefit from early detection through NBS and prompt ERT; however, timing and efficacy in treating the late-onset forms is unclear. Individuals with the late-onset forms might not show symptoms for decades and the benefit from early identification is unknown. Moreover, individuals with symptomatic Gaucher disease clearly benefit from therapy; however, at least half of individuals with Gaucher disease remain asymptomatic throughout life. NBS for most LSDs would not distinguish between early and late-onset forms, or potentially symptomatic and asymptomatic individuals. Population-wide screening for LSDs would include pre-symptomatic testing for adult-onset conditions that is routinely discouraged by clinical practice guidelines. The lack of data on psychosocial implications of identifying individuals with adult-onset variants through NBS has been highlighted (Kemper et al., 2007).

Even among those with early onset variants, ERT itself is an expensive, time-consuming, and lifelong treatment. Families without insurance or adequate coverage may be faced with forgoing life-saving therapy for their child. If NBS for LSDs is identified as an important public health goal, are we – as a society – committed to covering treatment costs for affected individuals? If not, what are the psychosocial implications of early diagnosis among families who cannot afford to provide treatment for their child? How do we counsel and support families whose infant is diagnosed with a late-onset variant? These are among the questions health-care providers and the medical care system will be forced to answer in the not-so-distant future. In fact, NBS for Krabbe disease, a rare and uniformly fatal LSD affecting the central nervous system, was implemented in New York in 2006, and >260,000 newborns have now been screened. Two newborns, with a high-risk genotype and low enzyme activity, have been identified and undergone stem cell transplant with umbilical cord blood, an effective therapy for pre-symptomatically identified individuals (Caggana, Saavedra, Wenger, Helton, & Orsini, 2008). One newborn, however, died as a result of the transplant, a known complication in approximately 10% of cases (Martin et al., 2006).

NBS also can identify carriers of genetic conditions. Carriers are individuals who have a mutation on only one copy of a gene but are themselves unaffected. Testing children for genetic carrier status has been generally discouraged (ACMG Position Statement, 1995). And yet, NBS for hemoglobinopathies like sickle cell disease has been estimated to identify 17–100 carriers for every affected infant (Laird et al., 1996). The same risk for carrier identification applies to NBS for CF, now implemented throughout much of the United States. This has important consequences not only for the patient who was unable to consent to testing but also for parents

who are often unfamiliar with the consequences of being a carrier for a genetic disorder. For example, one study from the Wisconsin CF NBS program found that 15.4% of parents surveyed were not sure whether or not carrier status would cause illness (Ciske et al., 2001).

Advances in microarray DNA chip technology are pushing the envelope for NBS even further, allowing for direct mutation analysis of hundreds of genes at once, using a single blood sample. These are generally "untreatable" conditions, with no available dietary interventions or enzyme replacement therapies known to improve outcome. Arguments against testing newborns for hundreds of single gene disorders include the lack of known treatment protocols and the absence of data supporting a proven benefit to early diagnosis, as well as the above-listed concerns related to the identification of carrier status and late-onset conditions. However, arguments in favor of screening for "untreatable" conditions (e.g., FXS and DMD) have also been presented and include the benefit of timely early intervention services or supportive therapies; the avoidance of a costly, lengthy diagnostic odyssey with attendant risks from invasive procedures or iatrogenic complications; and increased reproductive knowledge for families (Ross, 2006). Much of the disagreement about expanded NBS may be, at its heart, a difference in opinion about the goals of NBS and our ability to support patients and their families who are impacted by this technology. In the end, our society must weigh the risks, costs, and benefits of early diagnosis and management of children with single gene disorders identified through NBS.

FUTURE DIRECTIONS

It is not a question of whether or not NBS for single gene disorders will expand in the future; it undoubtedly will. Although some health-care providers may caution against expanded screening, the general public, public health, and medical communities continue to express support (Botkin et al., 2006; Quinlivan & Suriadi, 2006; Skinner et al., 2003). As a result, private laboratories will be persuaded to offer expanded screening to families, regardless of concerns voiced by health-care professionals. In some ways, the future is already here. Pediatrix, a private NBS company, currently markets testing for a panel of over 50 disorders both to hospitals and directly to parents (http://www.pediatrix.com). How will we meet the challenges of both timely and effective medical follow-up for identified newborns in public health screening programs?

An area of discussion surrounds who should be responsible for short- and long-term follow-up of presumptive positive individuals. Short-term follow-up refers to ensuring that all infants are adequately screened. This is generally the responsibility of state health departments and is fairly well established (although not without its flaws). The larger concern surrounds long-term follow-up of affected individuals. Who will be responsible for care and management? Similar to early screening for PKU, little is known about the natural history and treatment of many metabolic disorders on the NBS panel. Prior to NBS, most individuals with such conditions

died in infancy or had significant cognitive and/or physical impairments. Affected individuals are now living into later adolescence and adulthood, and questions remain about how best to serve this growing population and recognize their needs.

Unfortunately, despite advances in human genetics, few changes have been made in medical school education. Throughout the United States, medical school programs continue to devote little time to genetics; generally, the myriad of complex issues related to genetics and genetic testing is addressed in one or two introductory courses during the first or the second year. The vast majority of trainees who choose not to specialize in genetics are then relegated to learning more through elective coursework or continuing education. The speed at which genetics knowledge progresses limits the benefit of the apprenticeship model of training, as more experienced practicing physicians will not likely be up-to-date with current issues in genetics. Given this model, it is not surprising to find pediatricians' knowledge of genetics severely lacking. One study found that 20% of pediatricians and 50% of family physicians did not feel comfortable discussing PKU with families after a positive test result (Kemper, Uren, Moseley, & Clark, 2006). This is especially alarming given that PKU has been part of the NBS panel since the 1960s. Clearly, more education and training are needed before long-term management of individuals with single gene disorders enters primary care.

Despite their limited genetics training, pediatricians and primary care providers are increasingly called upon to interpret abnormal NBS results and counsel families about possible outcomes. Referral to a medical geneticist for additional evaluation and management is indicated and of proven benefit to the family, but not always possible. In light of genetics specialist shortages, pediatricians must provide first-line counseling to anxious parents regarding abnormal screen results, which could indicate a potentially life-threatening genetic disorder. As described throughout, this can lead to increased anxiety, altered bonding, and unnecessary worry about child's health status. Educating primary health-care providers about NBS and follow-up care is among the research initiatives outlined by the National Institute of Child Health and Human Development (Alexander & Hanson, 2006). As part of an initiative under the Maternal and Child Health Bureau of the Human Resources and Services Administration, the American College of Medical Genetics developed ACT sheets for conditions recommended as part of the uniform NBS panel (2007). According to the ACMG website: "for each marker(s), there is (1) an ACTion (ACT) sheet that describes the short term actions a health professional should follow in communicating with the family and determining the appropriate steps in the follow-up of the infant that has screened positive, and (2) an algorithm that presents an overview of the basic steps involved in determining the final diagnosis in the infant" (http://www.acmg.net/resources/policies/ACT/condition-analyte-links.html). This is a step in the right direction toward educating primary care providers about NBS, yet it does not ensure that all families will receive appropriate and timely counseling regarding NBS results. Importantly, it does not encompass information about the psychological

implications associated with NBS for single gene disorders, which are important to understand given downstream effects on family functioning and medical and psychological health of the child.

Early diagnosis of affected individuals through NBS has a number of proven medical and psychosocial benefits for patients and their families. As has been shown since the 1960s, early detection of treatable inborn errors of metabolism can effectively reduce morbidity and mortality of patients. Even among conditions that do not meet the established criteria for NBS, it has been advocated as a means to earlier enrollment in intervention services and decreased parental anxiety surrounding the diagnostic odyssey (Bailey, 2004). A long-term negative impact on quality of life or self-concept for individuals diagnosed through NBS has not been documented; however, the few available studies are limited.

What are also clear are the potential consequences of false-positive results on the patient and family. Inadequate patient education and counseling and support of families during this initial crisis period can result in increased parental anxiety leading to actual negative health and behavioral outcomes for the child. More research is needed to explore what, if any, affect false-positive results have on parents, especially fathers. Increased knowledge about NBS, counseling, and referral to a metabolic specialist and/or a genetic counselor has been associated with a decrease in parental stress following repeat NBS. However, this is not always feasible, given time and geographic limitations. One possibility is to more fully integrate genetics professionals into subspecialty departments, including cardiology, endocrinology, and neurology. This could increase referral to genetics professionals through greater accessibility to providers and help educate subspecialists about psychosocial implications of diagnosing children with single gene disorders. It is possible that providers with direct links to a genetics professional who is knowledgeable about their specific area of medicine will be more likely to refer for additional counseling and seek information about medical and psychological implications of genetic testing for single gene disorders. Geographic limitations could be overcome through video conferencing between remote locations and more metropolitan medical centers.

Areas of future research include not only natural history studies of conditions diagnosed through NBS but also studies on the experiences of families with false-positive and true-positive results, the long-term impact on child physical and mental well-being, and focused interventions on parental stress and anxiety related to false-positive results. Discussion on the various “goals” of NBS as a public health initiative is needed. There must be a contemporary, agreed upon structure and end points for NBS, otherwise we place ourselves on a slippery slope. Should NBS for all known genetic disorders be offered simply because the technology is available? Is the possible impact on reproductive decision making and enrollment in early intervention services or research trials enough to justify the risk associated with thousands of false-positive or ambiguous results? Answers to these important questions remain to be seen.

Beyond the context of NBS, expanded exploration of the psychological implications of genetic testing for single gene disorders is needed to

better understand the impact on patients and their families. Specifically, the role of hope and optimism in adaptation is an interesting area of future research. In tandem, interventions that increase family functioning and support healthy adaptation should be rigorously examined. This will allow clinicians to translate social and behavioral research findings into interventions to promote improved outcomes for patients and families.

Ultimately, a balance needs to be struck between the public health goal of reducing morbidity and mortality among patients with single gene disorders and avoiding unnecessary psychological risks to families and the health-care system at large. The questions we need to answer before this balance can be reached are both numerous and complex. Further discussion is needed among primary care providers, genetics professionals, psychologist and scientists, patients, and their families to move this issue forward in a socially and medically responsible manner.

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11

Hereditary Cancer Risk

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The elucidation of the sequence of the human genome promises to usher in a new era of medicine that will result in improved diagnosis and identification of individuals at risk for hereditary conditions. In this chapter, we focus on genetic testing for hereditary cancer risk in children and families and how such testing impacts the management of children with a diagnosis of cancer or who are at risk for cancer. We provide descriptions of the major hereditary cancers and cancer syndromes affecting children, as well as cancer predisposition syndromes that occur primarily in adulthood, but for which testing in minors has been raised as consideration. The impact on children's medical management will be reviewed, as well as data on the psychosocial effects of testing. It is important to note that a hallmark feature of an inherited predisposition to cancer is that affected individuals are usually at high risk of developing more than one type of malignancy; thus, screening and risk reduction guidelines are often targeted to more than one site or system. Because of the potential for considerable morbidity and mortality arising from hereditary cancers, the psychosocial impact may be significant for the individual and family.

As alluded to above, one facet of genetic testing that distinguishes it from most medical tests is that a positive result (i.e., the identification of a gene mutation) has implications not only for the individual tested but also for his or her immediate and often extended family. In the context of cancer genetic testing, we will explore two aspects of this phenomenon. The first is how genetic testing impacts children and the family unit, and the second is how a parent's own experience with cancer and the process of communicating genetic testing results for cancer predisposition may affect the child and the parent–child relationship. We will then briefly extend the discussion about controversial issues in predictive testing in children as it is relevant to cancer susceptibility testing. Finally, we will speculate about future trends and research in this ever-evolving arena of risk assessment,

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particularly with the rise of direct-to-consumer genetic testing, pharmacogenetics, and the increasing availability of bundled testing for multiple gene alterations associated with various traits and conditions.

HEREDITARY CANCERS, CANCER SYNDROMES, AND CONDITIONS FEATURING MALIGNANCIES AFFECTING CHILDREN

Most cancers that develop in children are not hereditary. However, it is important to be aware of which childhood cancers, syndromes, and conditions with malignant features have a hereditary component, as genetic testing and medical management for the affected child as well as at-risk siblings and other relatives will be impacted. These conditions are briefly described below. There are also several cancer syndromes with malignant or neoplastic features that can occur in children; however, in many of these syndromes, defining features may not manifest until adulthood. These cancer syndromes are summarized in Table 1.

Nonsyndromic Cancers

Two primarily nonsyndromic childhood cancers which may be hereditary are retinoblastoma (RB) and Wilms tumor (WT) (Pakakasama & Tomlinson, 2002; Strahm & Malkin, 2006). RB accounts for up to 4% of all childhood cancers and is caused by mutations in the *RB1* gene. The incidence is 1 in 15,000, with a median age at diagnosis of 22 months. Hereditary RB comprises approximately 40% of all RB and has an average age at diagnosis of 15 months. The lifetime risk with hereditary RB is 90%, and it often presents with bilateral or multifocal unilateral disease.

Sensitivity for detecting *RB1* mutations is greater than 90%. Nearly 100% of children with RB and a positive family history will have an *RB1* mutation, regardless of presentation. Similarly, greater than 90% of children with bilateral RB will have an *RB1* mutation, regardless of family history. Among children with unifocal, unilateral retinoblastoma who have no family history, approximately 10–15% have an *RB1* mutation.

Most individuals with RB have de novo mutations. However, mutation carriers, or family members known to be at risk for a mutation, should undergo ophthalmologic exam under anesthesia every 3 months, beginning shortly after birth. Genetic testing is integral to determining if such screening is necessary. Another issue is the risk for secondary tumors, particularly osteosarcomas, soft tissue sarcomas, and/or melanomas (Tischkowitz & Rosser, 2004). The risk for a secondary cancer is very high for survivors of RB, which is further increased for those who underwent radiotherapy. Thus, genetic testing allows for early detection of retinoblastoma, potentially permitting non-radiation-based treatment.

Wilms tumor accounts for approximately 7% of all childhood cancers, with an incidence of 1 in 10,000 (Tischkowitz & Rosser, 2004). Most cases are sporadic, with only a small percentage due to identifiable germline

Table 1. Hereditary Cancer Syndromes with Manifestations in Childhood or Young Adulthood

Syndrome; Gene	Incidence; Inheritance	Malignancies (Predominant)	Malignancies (Rare)	Non-malignant Neoplasms	Non-neoplastic Manifestations	Select Medical Management Issues	References
Endocrine syndromes							
Multiple endocrine neoplasia type 1 (MEN1); *MEN1*	1/30,000; autosomal dominant; de novo rate: 10%	Entero-pancreatic islet cell tumors (e.g., gastrinomas 40%)	Pancreatic insulinomas (10%); thymic carcinoid (2%); bronchial carcinoid (2%)	Parathyroid adenoma (90%); anterior pituitary tumors (20–60%); facial angiofibromas (90%); collagenomas (75%); adrenocortical (20–40%); lipomas (10–30%); meningiomas (8%); ependymoma (1%); pheochromocytoma (<1%)	Hyperparathyroidism (95–100%)	Syndrome penetrance is 50% by age 20 and >95% by age 40 Biochemical screening beginning at age 5–8 years, gastrin screening added at age 20; imaging with head MRI from age 5 and abdominal CT or MRI from age 20	Brandi et al. (2001), Lairmore et al. (2004)
Multiple endocrine neoplasia type 2 (types 2A and 2B and familial medullary thyroid cancer, FMTC); *RET*	1/30,000; autosomal dominant; de novo rates: 2A: 5%; 2B: 50%; FMTC: 0%	Medullary thyroid cancer (MTC; 2A: 95%; 2B and FMTC: 100%)	None	2A: pheochromocytoma (50%); parathyroid disease (20–30%) 2B: pheochromocytoma (50%); intestinal ganglioneuromatosis (40%)	2B: marfanoid habitus; mucosal neuromas of lips and tongue; "blubbery" lips; medullated corneal nerve fibers	All subtypes associated with nearly 100% penetrance of MTC Biochemical screening beginning at age 5 years; prophylactic thyroidectomy in early infancy or by age 10	Brandi et al. (2001), Cohen and Moley (2003)

(Continued)

Table 1. *(Continued)*

Syndrome; Gene	Incidence; Inheritance	Malignancies (Predominant)	Malignancies (Rare)	Non-malignant Neoplasms	Non-neoplastic Manifestations	Select Medical Management Issues	References
Colorectal cancer syndromes							
Familial adenomatous polyposis (FAP); *APC* or *MYH*	1/10,000; *APC*: autosomal dominant; *MYH*: autosomal recessive; de novo rates for both: 20 and 30%	Colorectal (~100%)	Duodenal (4–12%); thyroid (2–4%); pancreas (1–2%); hepatoblastoma (0.5–1%); medulloblastoma (<1%)	Colonic polyposis (100%); duodenal adenomas (50–90%); fundic gland retention polyps of the stomach (50%); desmoids (10%); osteomas (20%)	Multiple, bilateral CHRPEs (congenital hypertrophy of the retinal pigment epithelium); sebaceous cysts (20%); dental abnormalities (20%)	Colon polyps usually develop by age 15 in classic FAP. Annual or biannual endoscopy begins at 10–12 years. Prophylactic colectomy is usually performed in late adolescence to early adulthood. Periodic upper endoscopy is also recommended	Church and Simmang (2003), Sieber et al. (2003)

(Continued)

Table 1. *(Continued)*

Syndrome; Gene	Incidence; Inheritance	Malignancies (Predominant)	Malignancies (Rare)	Non-malignant Neoplasms	Non-neoplastic Manifestations	Select Medical Management Issues	References
Peutz–Jeghers syndrome (PJS); *STK11* (also referred to as *LKB1*)	1/200,000; autosomal dominant; de novo rate: 50%	Breast (45–54%); colon (39%); pancreas (11–36%); stomach (29%); small bowel (13%); lung (15%); ovaries (21%)	Cervix (10%); testes (9%); uterus (9%)	GI-tract hamartomatous polyposis (95% small bowel; 25% colon and stomach)	Small bowel intussusception; melanin pigmentation	Risk of intussusception is 68% by age 18. Lifetime cancer risk approaches 90%. Testicular screening begins at birth. Upper endoscopy and small bowel series begin at age 8, with colonoscopy at age 18. Gynecologic screening begins at age 21	Giardello et al. (2000), Giardello and Trimbath (2006), Hearle et al. (2006), Hinds, Philp, Hyer, and Fell (2004)
Juvenile polyposis syndrome (JPS); *SMAD4* and *BMPR1A*	1/100,000; autosomal dominant; de novo rate: 25%	Colorectal (39%)	Stomach; small intestine; pancreas	GI-tract hamartomatous polyposis (>90%)	Hemorrhagic telangiectasias (only with *SMAD4*)	Lifetime colorectal cancer risk is 39%. At age 15 or with onset of symptoms, annual blood tests, and colonoscopy every 2 years	Brosens et al. (2007), Jass, Williams, Buessey, and Morson (1988)

(Continued)

Table 1. *(Continued)*

Syndrome; Gene	Incidence; Inheritance	Malignancies (Predominant)	Malignancies (Rare)	Non-malignant Neoplasms	Non-neoplastic Manifestations	Select Medical Management Issues	References
Multisystem syndromes							
Li–Fraumeni syndrome (LFS); *p53*	Unknown; autosomal dominant; de novo rate: 25%	Sarcoma (soft tissue and bone); brain; breast; leukemia; adrenocortical	Lung; gastric; colorectal; pancreatic; Wilms tumor; malignant phyllodes tumors; choroid plexus carcinoma	None	None	Lifetime risk of cancer is 73% for males and 100% for females. Children are at high risk of adrenocortical cancer, sarcoma, and brain cancer. Childhood screening (e.g., blood and urine tests) may be considered. Breast cancer screening in women by age 20–25	Chompret et al. (2000), Olivier et al. (2003)

(Continued)

Table 1. *(Continued)*

Syndrome; Gene	Incidence; Inheritance	Malignancies (Predominant)	Malignancies (Rare)	Non-malignant Neoplasms	Non-neoplastic Manifestations	Select Medical Management Issues	References
Von Hippel–Lindau syndrome (VHL); *VHL*	1/36,000; autosomal dominant; de novo rate: 20%	Renal cell carcinoma (40%)	Pancreatic neuroendocrine tumors (5–10%)	CNS hemangioblastomas (80% brain and 20% spinal); retinal angiomas/hemangioblastomas (70%); epididymal cystadenomas (50%); pheochromocytomas (10–20%); endolymphatic sac tumors (10%)	Renal cysts (75%); pancreatic cysts (15–50%)	Most major features manifest by the twenties; penetrance is virtually complete by age 65. Annual ophthalmologic exams begin by age 5, as may annual blood pressure screening. Annual abdominal ultrasound begins at age 16	Kreusel, Bechrakis, Krause, Neumann, and Foerster (2006), Priesemann et al. (2006)

(Continued)

Table 1. *(Continued)*

Syndrome; Gene	Incidence; Inheritance	Malignancies (Predominant)	Malignancies (Rare)	Non-malignant Neoplasms	Non-neoplastic Manifestations	Select Medical Management Issues	References
Nevoid basal cell carcinoma or Gorlin syndrome (NBCC); *PTCH1*	1/40,000; autosomal dominant; de novo rate: 20–30%	Basal cell carcinoma (BCC) (90%)	Medulloblastoma (5%)	Ovarian fibromas (20%); cardiac fibromas (2%)	Calcification of the falx (>90%); jaw keratocysts (90%); macrocephaly and facial gestalt (60%); palmar/plantar pits (65–85%); skeletal (40–60%) and other congenital anomalies (5%)	Median age of BCC is 25 years, but can occur in childhood. Jaw keratocysts and calcification of the falx may occur in adolescence. Skin exams and screening for jaw cysts begin in childhood	Evans, Ladusans, Rimmer, Burnell, Thakker, and Farndon (1993), 2007), Gorlin (2004)

mutations or syndromes. Bilateral tumors are more prevalent with genetic predisposition syndromes, though only 5–10% of all children with WT have such a syndrome.

The gene associated with WT is *WT1*; however, *WT1* mutations in familial cases occur rarely (less than 1%). Several congenital syndromes predispose to WT, including WAGR (Wilms tumor, aniridia, genital anomalies, and retardation), Denys–Drash syndrome, and Beckwith–Wiedemann syndrome. For each, diagnosis is generally based on clinical findings rather than genetic testing. Recommended screening for individuals at increased risk for Wilms tumor includes abdominal ultrasound every 3 months until age 7 years (Pakakasama & Tomlinson, 2002).

Chromosome Instability Syndromes

Several well-defined chromosome instability syndromes exist, including ataxia telangiectasia, Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, Rothmund–Thomson syndrome, Werner syndrome, and xeroderma pigmentosum (Strahm & Malkin, 2006). These syndromes are all characterized by deficient DNA repair mechanisms and often have characteristic chromosomal abnormalities. Multiple congenital anomalies may be present at birth, and the incidence of a variety of cancers is greatly increased (e.g., lymphomas, leukemias, and other malignancies). Intensive screening protocols are initiated at an early age so that proper therapy can be initiated as early as possible. Cancer treatment is compromised due to increased radio- and chemo-sensitivity of non-neoplastic tissues, generally resulting in poorer prognosis and early mortality.

Each of the chromosome instability syndromes is inherited in an autosomal recessive pattern, so the affected child is often the first family member to have the condition. Molecular genetic testing permits diagnosis of affected siblings that may not be readily apparent due to syndrome heterogeneity. As is typical of recessive inheritance, carrier parents are generally unaffected. There are two exceptions to this: one, heterozygous female carriers of *ATM* gene mutations are at increased risk for breast cancer, which is significant since the carrier rate is 1 in 100, and two, the *FancD1* subtype of Fanconi anemia is the *BRCA2* gene, which dramatically increases the risk for breast and ovarian cancers in adult women (Pakakasama & Tomlinson, 2002; Strahm & Malkin, 2006).

Other Genetic Conditions with Malignancy Risks

Finally, there are several examples of genetic conditions for which cancer is not a defining feature, but for which malignancy may be a major cause of morbidity and mortality. The conditions discussed in this section are Down syndrome (DS), neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), and Beckwith–Wiedemann syndrome (BWS).

Down syndrome (DS), also known as trisomy 21, is one of the most common chromosome aberrations in humans, occurring in about 0.5% of all conceptuses and 1 in 900 live births (Cummings, 2003). In

addition to characteristic physical features including epicanthic folds, hypotonia, a wide skull, and furrowed tongue, affected individuals are mentally retarded and may have serious cardiac defects (Cummings, 2003). Children with DS have a 10- to 20-fold increased risk of leukemia and as much as a 500-fold increased risk for acute megakaryoblastic leukemia (AML-M7) in particular (Ross, Spector, Robison, & Olshan, 2005). Children under the age of 5 years have the highest risk of leukemia (Ross et al., 2005). Thus, even though the average life span for individuals with DS is increasing, the occurrence of cancer may lead to early mortality (Ross et al., 2005). Most cases of DS occur sporadically; however, when a parent is a carrier of a balanced translocation, recurrence risks for future children are increased; in addition, relatives (e.g., siblings) of the parent carrying the translocation also have elevated risks for having an affected child (Cummings, 2003).

Neurofibromatosis type 1 (NF1) affects approximately 1 in 3,000 individuals, with about half occurring as de novo mutations. Many children will first come to clinical attention due to having multiple café-au-lait spots. Analysis of the *NF1* gene is available and 95% sensitive, but diagnosis is almost always made using the NIH consensus criteria (NIH Consensus Development Conference, 1988). In addition to neurofibromas, iris hamartomas, and other diagnostic features, NF1 is associated with learning disabilities (30–60%) and attention-deficit hyperactivity disorder (40%), though mental retardation is rare.

Optic glioma is present in 10–15% of people with NF1, and though generally non-malignant, it can impinge on the optic nerve. It is most common in children up to age 6 years, and annual ophthalmologic exam is recommended from birth to as late as age 10 years (Gutmann et al., 1997). There is also an approximate 10% risk to develop a malignant peripheral nerve sheath tumor (MPNST), which arises in plexiform or subcutaneous neurofibromas and can metastasize widely. Other reported malignancies, though rare, include pheochromocytomas, gastrointestinal stromal tumors (GIST), brain tumors, and leukemia. In addition, one study reported that women less than age 50 with NF1 have a fivefold increased risk of breast cancer; thus, heightened screening, including mammography beginning at age 40, should be considered (Sharif et al., 2007).

Neurofibromatosis type 2 (NF2) affects 1 in 25,000 individuals, with about half occurring as de novo mutations. Although disease severity varies between families, it is usually very consistent within a specific family. Bilateral vestibular neuromas (schwannomas) are pathognomonic for the syndrome and can cause deafness, tinnitus, and balance disturbance. Most people are diagnosed between 18 and 24 years old, though pediatric diagnoses are sometimes made based on meningiomas or schwannomas (Evans et al., 1992).

Screening begins at birth, with regular pediatrician exams and awareness of symptoms (Evans et al., 2005). Beginning at age 10 years, annual ophthalmologic exams and brain stem auditory-evoked responses are recommended. From age 12 years onward, MRI of the central nervous system is recommended every 1–3 years. Despite close surveillance, NF2 is

associated with high morbidity and mortality, the major cause of which is cranial meningiomas. The median survival is 15 years after the first presenting symptom.

Tuberous sclerosis complex (TSC) is a highly variable, multisystem disorder with an incidence of about 1 in 6,000 (Curatolo, Bombardieri, & Jozwiak, 2008). Although it is inherited in an autosomal dominant fashion, approximately two-thirds of cases arise de novo. Mutations in two genes, *TSC1* and *TSC2*, are causative. This neurocutaneous syndrome, which may be diagnosed in infancy, is characterized by the presence of hamartomas, fibromas, and cysts and various benign tumors in the brain, kidneys, and heart. Although renal complications are the most frequent source of mortality in affected patients, elevated risks of cancer exist as well (Curatolo et al., 2008). Specifically, in childhood and early adulthood, there is a 5–14% risk of brain tumors, as well as increased risks of renal cell cancer and malignant angiomyolipoma (Offit, Sagi, & Hurley, 2006).

Surveillance in asymptomatic patients consists of neurodevelopmental testing, ophthalmic exam, renal ultrasounds, and other tests assessing brain and cardiac function. In addition, symptomatic management, especially for seizures, is important (Curatolo et al., 2008).

Beckwith–Wiedemann syndrome (BWS) affects 1 in 13,700 individuals, of which 85% are de novo and 15% familial, and diagnosis is generally made based on clinical findings (Pakakasama & Tomlinson, 2002). BWS is genetically complicated, as alteration of any one of a number of genes located at 11p15 can result in the syndrome. One to two percent of cases are due to visible chromosomal rearrangements while 10–20% are due to paternal uniparental disomy. Almost half of the familial cases are due to mutations in the *CDKN1C* gene.

Malignancies reported with BWS include Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma. The risk of malignancy is 7.5% up to age 8 years, but very rare after age 8 years. Recommended neoplasm screening includes quarterly abdominal ultrasound exam every 3 months until age 7 and measurement of serum alpha fetoprotein (AFP) concentration in the first few years of life for hepatoblastoma. Screening has also been proposed for neuroblastoma, but is not routinely performed due to low yield.

Hereditary Cancer Syndromes Affecting Children

A number of hereditary cancer predisposition syndromes can manifest in childhood. For each of the syndromes in Table 1, cancer is the predominant feature, risk of malignancy is dramatically elevated, and intervention in early childhood or even infancy may be recommended. The efficacy of medical management is well documented in several syndromes, including the multiple endocrine neoplasias and familial adenomatous polyposis, but unproven in others, such as Li–Fraumeni syndrome. Nonetheless, the risk of childhood malignancy is increased enough to necessitate consideration of genetic testing before adulthood.

With the exception of a variant of familial adenomatous polyposis, the syndromes listed in Table 1 are inherited in an autosomal dominant pattern, meaning that the children of an affected parent have a 50% chance of inheriting the mutated gene. Table 1 summarizes these syndromes, including the associated gene(s), principal malignancies, and non-cancerous features, and predominant medical management issues in children and young adults.

HEREDITARY CANCER SYNDROMES GENERALLY MANIFESTING IN ADULTHOOD

Cancer is much more common in adulthood than childhood, and the majority of adult-onset cancers, as with those seen in childhood, are sporadic. However, as many as 10% of adult-onset cancers are believed to be hereditary. Identification of a hereditary cancer syndrome can have implications for medical management of the patient with cancer, as well as dramatically impact screening and risk-reducing recommendations for at-risk relatives.

Hereditary syndromes that predispose to breast and ovarian cancer, colorectal cancer, melanoma, and gastric cancer are well delineated, and genetic testing for the major syndromes is available. As compared to the syndromes previously described in this chapter, malignancy is rarely observed in childhood. The average age at diagnosis of cancer is generally in the forties, and the earliest surveillance usually begins at age 20–25 years. These syndromes are inherited in an autosomal dominant pattern; thus, each child of an affected parent has a 50% of also having the predisposition. However, as management does not begin in childhood, in general, genetic testing should thus be deferred until the individual reaches adulthood and is able to make an autonomous decision. The issue of predictive genetic testing will be revisited later in this chapter.

Because breast and colon cancers are relatively common, familial clusters of these cancers are encountered frequently. However, the proportion of these families with a true inherited risk is under 10%. Most cases of hereditary breast cancer are attributable to mutations in the *BRCA1* or *BRCA2* genes. Mutations in these genes confer a 45–84% risk of breast cancer and a 11–62% risk of ovarian cancer, with a tendency for early ages at diagnosis, particularly for breast cancer (National Comprehensive Cancer Network, 2010). In addition, increased risks for prostate, pancreatic, and male breast cancer have also been observed. Screening and risk reduction options (e.g., with mammography and breast magnetic resonance imaging) are not recommended in women until age 25, and screening guidelines for men may not be appreciably different from those applicable to men in the general population, although some men may be candidates for mammography (National Comprehensive Cancer Network, 2010). Women may also consider risk-reducing surgery (i.e., mastectomy or oophorectomy) as well as options for chemoprevention (e.g., with tamoxifen).

Mutations in at least four genes have been associated with hereditary colon cancer vis-à-vis a syndrome known as HNPCC or hereditary nonpolyposis colon cancer. Mutations in the two major genes, *MLH1* and *MSH2*, are associated with a 70% lifetime risk for colorectal cancer and a 40–60% risk of endometrial cancer (Lindor et al., 2006). Colonoscopy typically begins at age 20–25 years, and research has shown that adherence to regular colonoscopy reduces cancer incidence and mortality (Järvinen et al., 2000).

An important clinical issue affecting survivors of cancers with a heritable etiology regards reproductive decision making. When fertility is retained in these individuals, there are many issues that adolescents and young adults may have to confront, including whether and when to have children and whether to utilize preimplantation and/or prenatal genetic testing to identify the risk status of their offspring (Offit et al., 2006). Because these decisions traverse many domains – psychosocial, ethical, and clinical – it is incumbent on health-care providers to appropriately and sensitively address these issues with patients and families.

Psychosocial Research

Childhood Onset

Most hereditary cancer syndromes are rare, and the ones that predispose to childhood cancers are among the rarest. As discussed above, the considerable morbidity and potential for early mortality can be devastating for families, and it is important for parents to be informed about the natural history of the syndrome or condition in order to provide them with anticipatory guidance and psychological support (Fanos & Mackintosh, 1999). Indeed, learning about the hereditary nature of a condition may help parents consider short- and long-term management and caretaking issues and also provide them with information for their other children including guidance on genetic testing (including carrier testing) and medical management. Because of the relative rarity of these conditions, most of the medical literature pertaining to psychological issues with childhood-related genetic testing is based on theoretical concerns rather than empiric data. However, there are data on the psychosocial effects of genetic testing in children for two syndromes in which predictive testing significantly impacts medical management, as discussed below.

Multiple Endocrine Neoplasia 2A (MEN2A). The medical benefits of genetic testing for MEN2A are well documented, including the efficacy of early intervention to prevent metastatic medullary thyroid cancer. However, the psychosocial effects of genetic testing for this syndrome during childhood have been studied only from the perspective of the parents. One of the first studies reported parents' difficulty in discussing the disease with their children, and that parents found it easier to discuss the medical aspects than the emotional ones (Cleiren, Oskam, & Lips, 1989). The most extensive research on the subject has occurred in the Netherlands by Grosfeld et al. (1996, 2000a, 2000b). A 1-year longitudinal

study showed that parental psychological distress, though present immediately after disclosure of genetic test results, was no longer prominent after 1 year (Grosfeld et al., 1996). The researchers went on to evaluate the pre- and post-test reactions of 47 parents (22 couples and 3 single parents) of 40 children (mean age of 6.2 years; range 2 months to 14 years) undergoing predictive genetic testing for MEN2A. Prior to testing (Grosfeld et al., 2000a), almost half of the parents did not understand autosomal dominant inheritance, and many did not understand that genetic testing was for predisposition rather than an actual cancer screening test. Approximately half of the parents were insecure about the genetic testing, expected an unfavorable genetic test result, and still desired clinical screening for their child even if he/she received a favorable genetic test result. After disclosure of the results, those who received an unfavorable result expressed resignation and relief for the certainty, but concern for their child's health (Grosfeld et al., 2000b). Those who received favorable results expressed not only relief but also confusion and disbelief. Many desired consultation with an endocrinologist for confirmation, and over one-quarter of the parents requested continued cancer screening for their children. Fifty-five percent of the favorable group questioned the reliability of the results versus 21% of the unfavorable group. Of note, distrust of the results and desire for continued screening were higher among parents with less education, a demographic factor that was also associated with increased mean scores on depression, anxiety, and psychological distress scales. This finding suggested that parents with less education may require additional counseling surrounding genetic testing of their children.

Familial Adenomatous Polyposis (FAP). As with MEN2, the medical benefits of genetic testing for FAP are well documented. However, several studies have also evaluated the psychological impact of genetic testing for this condition during childhood. A comparison of 31 mutation-positive children with 29 true-negative children showed that depression, anxiety, and behavior expression remained within normal limits in both groups, though there was a trend toward increased depression and anxiety in the mutation-positive group (Michie, Bobrow, & Marteau, 2001). No difference was noted in situational distress or behavioral problems, and only three children (all in the mutation-positive group) stated that they regretted having genetic testing. Almost all of the children in both groups perceived their health as good or excellent. The same researchers performed prospective follow-up of 31 children (16 mutation-positive and 15 true-negative) at two time points (mean of 8 and 33 weeks post-testing) and showed increased distress about FAP and anxiety in the mutation-positive group, though the scores remained within the normal range. Perception of risk of polyposis and confidence in the perception increased over the year, but anxiety and depression did not, indicating that increased understanding does not result in greater distress.

Codori, Petersen, Boyd, Brandt, and Giardiello (1996, 2003) also evaluated the short- and long-term psychological effects of presymptomatic genetic testing children for FAP. Short-term follow-up at 3 weeks and 1 year post-testing, overall, showed no significant changes in depression, anxiety, or behavior. Interestingly, however, mutation-positive children

with affected mothers (versus affected fathers) showed statistically significant increases in depression and anxiety. Thus, long-term follow-up was performed, with a mean time of 38 months post-disclosure. Psychological functioning remained within normal limits, and there was no long-term statistical or clinically significant decline in the children's psychological functioning regardless of genetic status, sex of affected parent, or follow-up time point. However, genetic status of siblings did have implications for psychological outcome. Mutation-positive children who had mutation-positive siblings showed significantly increased, but subclinical, depression, while mutation-negative children with mutation-positive siblings showed clinical elevations in anxiety. Of note, behavior problems decreased in mutation-positive and mutation-negative children if they had a mutation-positive sibling. It was concluded that additional support is likely needed in families with more than one mutation-positive child and in families with mixed genetic test results.

Recently, an Australian registry-based study (Andrews et al., 2006) surveyed 88 members regarding their viewpoints on genetic testing. The 18- to 35-year-old participants each had a diagnosis of FAP (molecular or clinical) or were at 50% risk for FAP based on family history. On average, the participants were 12 years old when they first learned about FAP and 21 years old at the time of genetic testing. However, when asked at what age they would choose to genetically test their own children for FAP, 42% chose at birth and 19% opted for early childhood. Only 18% chose 10–14 years old, which is the current age recommended by medical and genetic professionals. Interestingly, though, when asked at what age they would first discuss FAP with their children, 34% opted for early childhood while 42% selected 10–14 years old. Thus, the participants wanted to know their children's genetic status at very young ages, but did not want to burden the children with the information until applicable to their own medical care. It may be further extrapolated that these individuals do not view genetic testing of minors as harmful or disadvantageous. Of note, the participants also cited impact of FAP on their children as the area for which they lacked necessary information and had the greatest need for support, indicating that periodic follow-up genetic counseling could be beneficial since genetic counseling and testing typically occur at an age much younger than the age at which most people make reproductive plans.

Finally, Duncan et al. (2008) conducted semi-structured interviews with adolescents and young adults who previously underwent genetic testing for FAP or Huntington disease (the latter being a fatal neurologic disease with adult onset). The results confirmed theoretical concerns and also showed that the range of effects actually exceeds those speculated. As previously proposed, counterintuitive results also occurred. Specifically, a gene-positive result had benefits, such as strengthened relationships, ability to move forward, and clarity regarding important issues in life, while a gene-negative result had harms, such as flat affect, guilt, and feeling distanced from some family members. These benefits and harms illustrate the need to forewarn genetic testing candidates about the possibility of "intuitively contradictory" reactions. Finally, the genetic testing process,

itself, had its own benefits (empowerment, awareness of support services, improved family relationships) and harms (confronting the issue, stress on the family unit, lack of control, and interference with school). Importantly, this study clarified the psychosocial issues from the point of view of a young adult.

Adult Onset

The impact of predictive genetic testing on adults undergoing testing is an active area of research, primarily focusing on uptake of screening and risk reduction options and psychosocial outcomes. However, less is known about the impact of genetic testing for adult-onset cancer susceptibility syndromes on the family, as a whole, including the adolescent children of tested adults. To date, over 400,000 individuals have been tested for predisposition to the most common forms of inherited cancers, including *BRCA1*- and *BRCA2*-associated breast and ovarian cancer and colon cancer associated with hereditary nonpolyposis colon cancer (HNPCC) (Myriad Genetics Laboratories, 2010). In part because of the high uptake of testing for these conditions, and the fact that the finding of a deleterious mutation has significant implications for adult relatives' cancer risks and medical management, a considerable amount of research has examined patterns of family communication about genetic test results, generally indicating a high rate of disclosure to adult relatives, especially sisters (Hughes et al., 2002). However, data are beginning to emerge regarding family system characteristics, and how these may impact parental communication of genetic testing results to adolescent children and what role partner support plays in decision making and the process of communication.

For example, van Oostrom and colleagues (2007a) assessed several psychosocial outcomes among 96 individuals (from 45 families) seeking genetic testing for HNPCC compared with 175 individuals (from 96 families) seeking genetic testing for *BRCA1* or *BRCA2*. All individuals were from families with a previously identified gene mutation. In addition to illness perceptions, coping, and cancer-related psychological distress, they also measured family system characteristics. These included cohesion and adaptability, differentiation from parents, familial communication style concerning hereditary cancer, and perceived social support. Overall, the family system characteristics were similar between the two groups 6 months after results disclosure, but participants from HNPCC families reported significantly more open communication about hereditary cancer with a partner and children than did participants from *BRCA1/2* families. The authors attribute this finding to increased threat perception among *BRCA1/2* carriers and the desire to protect partners and children. One-third of participants reported positive changes in familial relationships, including improved relationships with children due to relief from a negative genetic test result (van Oostrom et al., 2007b). One-fifth of participants reported negative changes, including feelings of guilt about the possibility of passing down the mutation to children. Characteristics predictive of adverse consequences included enmeshed-chaotic or disengaged-rigid families (as determined at baseline), lack of

partner support, and less ability to freely communicate about hereditary cancer issues. There were no differences in reported changes between male and female respondents, but HNPCC participants reported significantly fewer changes with partners and parents than did *BRCA1/2* participants.

Several studies have begun to shed light on rates and predictors of parental disclosure of *BRCA1/2* test results to adolescent children, which appears to be relatively high even though there are no immediate medical implications to minors. Tercyak et al. (2001a) studied 133 men and women who underwent such testing, of whom 47% shared their mutation status with their children. Among mutation carriers, the rate of disclosure was not significantly different from the rate of nondisclosure to children (i.e., 53 versus 47%), whereas in noncarriers, 57% did not disclose their status to children. Overall, about 50% of parents chose to share their results with their minor children, regardless of the outcome. In a smaller study among 42 mothers who underwent *BRCA1/2* testing, the rate of disclosure to adolescent children within 1 month of obtaining test results was 53% (Tercyak, Peshkin, DeMarco, Brogan, & Lerman, 2002). The primary factors that were associated with disclosure were the age of the child (older versus younger) and the presence of an open parent–child communication style. Bradbury et al. (2007) identified similar rates of disclosure of parental *BRCA1/2*-positive test results and reported on parents' perception of children's comprehension, emotional response, and impact on the parent–child relationship. Although the sample size was small, it appeared that disclosure had relatively neutral effects on the latter two dimensions.

Increasing attention is being paid to the process of test result disclosure to children including the phases of decision making, decision conflict (if it exists), and communication between parents and children (Clarke, Butler, & Esplen, 2008). Aside from the parent–child relationship, the extent to which mothers engage their partners (i.e., non-tested fathers) in a discussion about disclosing to children and perhaps encourage fathers to participate in the disclosure process may also influence communication decisions and outcomes (DeMarco et al., 2008). For mothers who test positive for a cancer susceptibility gene mutation and who plan to undergo intensive surveillance and/or risk-reducing surgery, it is possible that disclosure of test results to children serves to alert and prepare them for steps that their mothers may be taking to reduce their cancer risks. Therefore, communication about genetic testing with fathers and children may also increase the support network for mothers. In addition to these influences on communication decisions, mothers, particularly those with higher decisional conflict about this issue, have indicated a strong need for resources to assist with decision making, which include literature about the topic, family counseling, access to prior testing participants faced with the same situation, and support groups (Tercyak et al., 2007).

An area of burgeoning research concerns the impact of parental disclosure on children's actual well-being (Tercyak, Peshkin, Streisand, & Lerman, 2001b). Bradbury et al. (2009) performed semi-structured interviews on 22 adult offspring who learned of their parent's positive *BRCA1/2* mutation status prior to age 25. Their data revealed that offspring had

varied recollections of the content of discussions about parental genetic test results, with more emphasis on cancer risks and genetic testing versus risk modification options. The majority did not report any negative reactions to learning this information, and there was high interest in genetic testing for themselves. Interestingly, in some instances, learning of the parents' mutation status fostered improved health behaviors such as smoking cessation. These qualitative data lay the groundwork for future studies investigating how individuals adapt to and incorporate information about genetic risk obtained as children or young adults and what factors may predict these outcomes.

Another relevant point to consider in the context of communication to children about genetic risk is the impact of a parent's cancer diagnosis on the adaptation of children in the short and long term. In many families with cancer, the first individual to undergo genetic testing has already been diagnosed with this disease. Because many of the syndromes affecting adults are associated with a relatively early age at diagnosis, it is not uncommon for those affected by cancer to have young children whom they are actively parenting. The disruption in routines and parenting responsibilities can have several detrimental effects on children. For example, it has been reported that the children of mothers with breast cancer have psychological and stress response-related problems that are associated with poor family functioning, which can be exacerbated in the setting of maternal depression (Edwards et al., 2008). Adolescent daughters may be particularly at risk for adverse emotional responses. For example, data suggest that relative to girls whose mothers did not have breast cancer, those with affected mothers appear to have significant worry about their own future health and genetic risk for breast cancer (Cappelli et al., 2005). Further, a study by van Oostrom et al. (2006) showed that women who were 10–13 years old when their mother was affected by breast cancer are at higher risk for psychological distress during the genetic testing process and that having a parent affected with cancer resulted in higher cancer risk perception.

The studies discussed in this section provide useful insight into a new and expanding area of interest in cancer genetics. However, it is important to recognize that studies published to date are limited in several respects. Primarily, they reflect relatively small clinical sample sizes from highly select populations, which limit their generalizability. Moreover, their representativeness of the general population is also insufficient, particularly with respect to underserved populations and minorities (Oloparde, 2004). In addition, relative to test decliners, individuals who opt for testing may be of higher genetic risk and possess higher motivation to obtain genetic information for their relatives (Armstrong et al., 2000). Those who opt for testing may also self-select based on their perceived ability to cope with testing positive; thus, prior to genetic counseling, they may have less psychological distress or be less concerned about the psychological effects of testing compared to testing decliners (Godard, Pratte, Dumont, Simard-Lebrun, & Simard, 2007; Lerman et al., 1998). Finally, in several studies, objective measurement of psychological distress may be inadequate or inconsistent. This is primarily due to the lack of availability of more

sensitive and task-specific measures of psychological distress. On this latter point, the development or utilization of psychological instruments specifically designed for individuals undergoing genetic testing (see Cella et al., 2002) could remedy this situation, as would validated adaptations of currently available instruments.

Despite these limitations, these studies underscore the concept that genetic information may have a profound effect on the family unit as a whole and that young children may be especially vulnerable to the impact of a parent's cancer diagnosis, generating feelings that may persist through adulthood. Comprehensive genetic counseling provides an opportune time to inquire about and address psychological and family issues and to provide appropriate referrals and guidance as needed. In addition, genetics and allied professionals, including psychologists experienced in working with children and families, can draw from the vast literature addressing the impact of cancer on families to better understand the dynamics of their needs and communication patterns (Baumann, 2006; Firth, 2006).

PREDICTIVE GENETIC TESTING IN CHILDREN

Controversies and concerns over presymptomatic genetic testing in childhood are significant, thus prompting a variety of professional organizations, representing many countries, to develop position statements. A systematic review by Borry, Stultiens, Nys, Cassiman, and Dierickx (2006) identified 27 guidelines or position papers written between 1991 and 2005 that address this issue. These statements were written by 31 different groups (of which 12 were genetics societies) from the United States, Europe, Japan, Australia, and Canada. It was noted that the guidelines uniformly cite medical benefit as the main justification for genetic testing of a minor and absence of "immediate" or "timely" medical benefit as the main reason for deferral of genetic testing until adulthood. However, no guidelines provide a definition of immediate or timely. Additionally, the guidelines do not strictly set 18 years old as the cutoff and emphasize "flexible consideration" for age at testing by assessing competence to make a decision after detailed pre-test counseling.

The statement by the American Society of Clinical Oncology (ASCO, 2003) is one of the most relevant policies pertaining to the issue of genetic testing in minors for cancer susceptibility. ASCO supports genetic testing only in the setting of extensive pre- and post-test counseling and maintains that providers ordering genetic testing must be prepared to facilitate a detailed, individualized discussion of screening, treatment, chemopreventive, and surgical risk-reducing options, including the efficacy (or lack thereof) of each option. ASCO has also established 12 basic elements of informed consent that are part of the genetic counseling and testing process. Regarding genetic testing of children, ASCO's position is that genetic testing *should* be offered when screening and/or prevention is available and recommended during childhood (e.g., FAP or MEN), *should not* be offered when the risk is low and no intervention is recommended during

childhood (e.g., *BRCA1/2*), and *may be carefully considered* when cancer risk is increased in childhood, though there may not be validated management recommendations (i.e., Li–Fraumeni syndrome). ASCO also recognizes the role of parental authority, but emphasizes that the medical provider should advocate for the best interests of the child.

A growing literature has begun to examine parental attitudes about genetic testing in children. When a child has had cancer, it is understandable that parents may then wonder about risk for their other healthy at-risk children. In an early, small study of 47 mothers of pediatric oncology patients diagnosed 6–24 months previously, 36% indicated that they would be interested in obtaining a hypothetical cancer susceptibility gene mutation test associated with a 90% lifetime risk of cancer – but only if there were medical benefits to know the information (Patenaude, Basili, Fairclough, & Li, 1996). Forty-nine percent of mothers would want their healthy children tested if there was medical benefit. Interestingly, regardless of potential benefit, a majority of mothers (51%) would be interested in testing for themselves and their healthy children (42%). Many mothers thought that the children's views about testing should be factored into decision making, particularly for older children, and that the age of the child similarly affects whether they should be informed about the results of testing (Patenaude et al., 1996). The study described above did not use concrete examples of conditions for which genetic testing yields clear medical benefits and for which testing is now part of routine clinical care, such as FAP and MEN. By contrast, predictive testing in children for adult-onset cancers such as breast and ovarian cancer is highly controversial and has been performed infrequently (Borry, Goffin, Nys, & Dierickx, 2008; Duncan, Savulescu, Gillam, Williamson, & Delatycki, 2005). A parent's decision to be tested is often motivated by a desire to learn about relatives' risks, and the decision to disclose results to minor children has been shown to be associated with parental interest in having their minor child tested (Tercyak et al., 2002). With respect to *BRCA1/2* testing, Bradbury et al. (2008) conducted interviews with 53 mutation carriers (predominantly mothers) and 22 of their adult children. They found that a majority of tested parents opposed *BRCA1/2* testing for their minor children (52%). However, 24% of the study participants believed that testing could be considered in some minor children. An important consideration in the case of *BRCA1/2* testing is that mature minors, in particular, may be interested in predictive testing to help make future decisions about childbearing and risk-reducing options (Bradbury et al., 2008). Recent case reports underscore that there is nothing magical about a child turning age 18 to provide an easy one-size-fits-all resolution to the issue of when it is appropriate to offer testing (Gaff, Lynch, & Spencer, 2006). A newly validated scale, the Pediatric *BRCA1/2* Testing Attitudes Scale (P-TAS), can be used to systematically assess evolving attitudes of parents about *BRCA1/2* testing in their minor children (Peshkin et al., 2008). Given the increasing amount of discussion about predictive testing in children, coupled with a rapid pace of gene discovery, it seems likely that, over time, requests for testing in minor children will increase. In order to ensure the child's autonomy, and to minimize potential harm, it is important for genetics and other

health-care professionals to work closely with families to carefully assess each person's interests and values, to foster informed decision making, and to develop short- and long-term plans that are consistent with current standards of practice and which address the needs and concerns of the family.

FUTURE DIRECTIONS

Advances in genomic medicine have elucidated the hereditary basis for several cancers that occur in childhood and cancer syndromes affecting adults. Research and clinical experience with children and their families have helped us to better understand how families communicate, assimilate, and manage information about cancer and genetic risk, but there is still much about these processes that remains uncharted. The practice of comprehensive pre- and post-test genetic counseling can be instrumental in helping individuals anticipate the effects of genetic testing and assisting them in identifying resource and support needs in the short and long terms. In light of this, genetics and other health-care professionals may need to consider expanding their services to include more integrated discussions of family issues and involving adolescents in the genetic counseling process, as appropriate. Meanwhile, ongoing research will address questions about the most effective ways to help individuals and families with decision making and support related to genetic testing. As the accessibility of genetic testing becomes broader (e.g., through direct-to-consumer testing via the Internet) and potentially more comprehensive in scope (e.g., including bundled tests for a variety of predispositions or conditions) (Offit, 2008), helping individuals and families understand the benefits, limitations, and implications of this information will become even more challenging. However, health-care providers can work together to help ensure that individuals and family members make autonomous, fully informed decisions about issues related to genetic testing, with the hope that they will be satisfied with those decisions and maximum benefits will be obtained.

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12

Type 1 Diabetes Risk

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Type 1 diabetes (T1D), usually diagnosed in childhood, is a lifelong chronic disease requiring daily insulin injections for survival. Also called childhood or juvenile diabetes, T1D is one of the most common chronic diseases of childhood, affecting approximately 1 in every 523 US children (SEARCH for Diabetes in Youth Study Group, 2006), and is increasing worldwide (DIAMOND Project Group, 2006). It is more common in non-Hispanic white children and least common among Asian, Pacific Island, and American Indian children. It can be diagnosed at any age but occurs most often during elementary school or early teen years (Rewers et al., 2008). T1D is an autoimmune disease in which the pancreatic beta cells responsible for insulin production are destroyed. Without insulin, the body cannot store glucose derived from food or drink. The patient loses weight despite eating sufficient calories and glucose in the blood accumulates resulting in high blood glucose levels or hyperglycemia. If untreated, the patient will begin to starve and break down body fat in response. This leads to a buildup of ketones in the blood which can lead to coma and death (Kaufman, 2008).

To survive, a patient with T1D must receive insulin by injection multiple times per day or by delivery through an insulin pump. Since current methods of insulin delivery only approximate normal pancreatic function, maintaining near-normal blood glucose levels is difficult. Both hyperglycemia and excessively low blood glucose levels – called hypoglycemia – can and do occur. Patients are asked to test their blood glucose levels multiple times a day and make insulin or dietary adjustments in response to blood glucose testing results in an effort to maintain blood glucose levels as close to normal as possible. Blood glucose testing is done by sticking the patient's finger to obtain a small drop of blood which is then "read" by a blood glucose-testing meter. Since food increases blood glucose levels and exercise decreases blood glucose levels, both must be taken into consideration as the patient and family try to meet the challenge

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of maintaining the child's blood glucose levels in the near-normal range (Silverstein et al., 2005).

T1D is associated with many serious complications that begin to appear 15–20 years after diagnosis including blindness, kidney disease, leg amputations, and cardiovascular disease. These complications reduce the patient's quality of life and increase mortality; life expectancy of a patient with T1D is reduced by at least 15 years (Portuese et al., 1995). However, there is good evidence that maintaining blood glucose levels in the near-normal range significantly reduces the risk of complications (Diabetes Control and Complications Trial Research Group, 1993). As a result, there is great pressure on patients and providers to maintain "tight" glycemic control which can be very difficult to accomplish (Nuovo et al., 1999).

New types of insulin and better insulin delivery and blood glucose-monitoring systems continue to be developed which hold promise for better glycemic control. Better methods to treat the complications of T1D continue to emerge, improving the quality of T1D patients' lives. Nevertheless, a "cure" for diabetes remains elusive. At the same time, a number of scientific breakthroughs have increased interest in disease prevention. Conceptualizing T1D as an autoimmune disease led to the discovery of islet cell autoantibodies (ICAs) in the blood of individuals before diagnosis, permitting identification of persons at high risk for developing T1D before disease onset (Achenbach, Bonifacio, Koczwara, & Ziegler, 2005). Genetics have long been presumed to play a causal role due to the fact that individuals with T1D relatives are at increased risk for developing the disease themselves. However, the discovery of specific genes associated with T1D has enabled investigators to identify individuals at risk for T1D before disease onset (Dorman, McCarthy, O'leary, & Koehler, 1995), increasing the potential of disease prevention.

The role of genetic testing in T1D is both interesting and controversial. It plays a critical role in the scientific effort to understand the etiology and natural history of this disease. However, genetic testing – in the absence of meaningful prevention – raises a number of ethical and psychosocial concerns. Although scientists continue to test potential prevention strategies (e.g., Ludvigsson et al., 2008), to date, large-scale T1D prevention trials have failed (Diabetes Prevention Trial – Type 1 Diabetes Study Group, 2002, 2005). Consequently, genetic testing for T1D has yet to deliver any viable method to prevent the disease. This chapter will address what is currently known about genetic testing for T1D and the ethical controversy surrounding it. The available literature on the psychological impact of that testing on families will be reviewed and its implications for patient care, research, and health policy will be discussed.

THE GENETICS AND NATURAL HISTORY OF TYPE 1 DIABETES

T1D has long been considered a genetic disease because of the increased prevalence of T1D in relatives of T1D patients. Recent genetic studies of autoimmune disorders have identified the human leukocyte

antigen (HLA) region of chromosome 6, which controls the immune response, as the critical area for identifying genetic markers for T1D. The HLA-DR, DQ genotypes are particularly important. Approximately 95% of T1D patients have the DR3 and/or the DR4 genotype and a child with both is particularly susceptible (Dorman et al., 1995; Barker, 2006). However, only 5% of those with the highest risk genotype develop T1D by 15 years of age (Barker, 2006), although the risk is considerably higher – 20–25% – if the child also has a first-degree relative with T1D (Schatz, Krischer, & She, 2002). Even among monozygotic twins, the concordance rate for T1D is less than 50% (Dorman et al., 1995).

These data suggest that other factors determine whether a genetically at-risk individual goes on to develop T1D. A variety of environmental triggers have been proposed, such as viral and nutritional exposures. The presence of gene–environmental interactions may explain the observed relatively weak association between genetic risk and diabetes onset; T1D may only occur in genetically at-risk individuals in the presence of one or more environmental triggers.

Figure 1 depicts our current understanding of the development of T1D. Genetically at-risk individuals remain diabetes free unless exposed to an environmental trigger. If exposed, an autoimmune process begins to destroy the beta cells in the individual's pancreas. During this time, ICAs and other types of antibodies appear in the individual's blood. Over time, pancreatic beta cells continue to be destroyed and the individual enters a "pre-diabetes" state, showing blood glucose levels above normal. Finally, so many beta cells are destroyed that the individual's blood glucose levels reach criteria for T1D diagnosis: a blood glucose level in the fasting state of $\geq$126 mg/dl (Schatz et al., 2002).

Currently, the critical environmental triggers for T1D remain unknown. The National Institutes of Health (NIH) has initiated an international multisite natural history study, The Environmental Triggers of Diabetes in the Young (TEDDY), which has identified genetically at-risk infants at birth and is following them over time, collecting detailed information on potential environmental triggers – illness, diet, stress, to

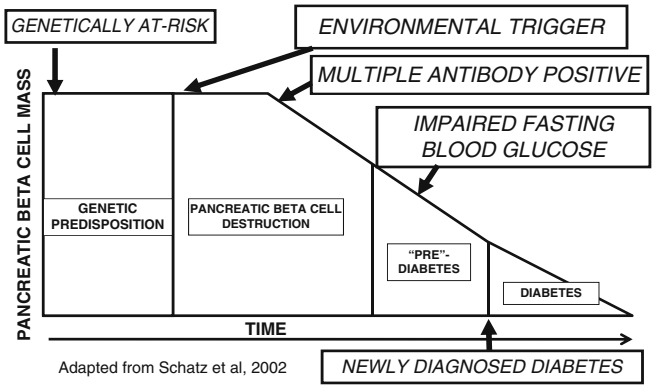

Figure 1. Model depicting the development of type 1 diabetes.

name a few (http://teddystudy.org). The hope is that this observational study will help scientists determine which environmental exposures are crucial for the development of T1D in genetically at-risk individuals. With this information, disease prevention may be possible.

GENETIC TESTING FOR T1D: ETHICAL ISSUES

Because there is no known method to prevent T1D in genetically at-risk individuals, genetic testing for T1D risk has sparked considerable controversy. The controversy has been heightened by the fact that most individuals screened for T1D risk are infants or young children. Due to the fact that infants and young children do not have the cognitive capacity to make their own decision about genetic testing, parents make this decision for them. Parents who decide to have the child genetically tested and learn if the child is at risk for T1D face added burdens of knowing the child is at risk with no means to prevent the disease and having to inform the child of the increased risk when the child is older.

The poor predictive power of T1D genetic testing poses additional challenges. Most children who are at increased risk for T1D will never get the disease. Many parents, and certainly children, will have difficulty understanding what "increased risk" means. The uncertainty associated with a positive genetic test result coupled with no known means to prevent T1D may cause considerable distress, including worry about an unpredictable, uncontrollable, impending disease. Concerns about possible insurance discrimination, especially in the United States, have been raised; certain insurance companies may view an individual's at-risk genotype as a "pre-existing" condition and deny insurance coverage should T1D occur.

Some have argued that genetic testing of children is justified only when the risk of disease is modifiable (Almond, 2006). Others have argued that T1D genetic test results should not be disclosed to participating families or that only children with a T1D relative should be offered such tests (Ross, 2003). Most agree that if genetic testing for T1D risk is to be conducted, it should be limited to carefully monitored research studies that rigorously protect the privacy of participants (American Academy of Pediatrics, 2001; Johnson, 2001; Roth, 2001; Weber, 1997). Those who conduct such studies have cogently argued that unless genetically at-risk children are identified and monitored, the environmental triggers of T1D will remain unknown, and the promise of disease prevention will never be realized despite major advances in our understanding of the genetic underpinnings of this disease (Schatz et al., 2002).

PSYCHOSOCIAL IMPACT OF T1D GENETIC TESTING

A number of investigators worldwide have begun studies of infants and children at risk for T1D. These include PANDA in north Florida and Georgia (Schatz et al., 2002), DAISY in Colorado (Rewers et al., 1996),

DEWIT in Washington State (Wion et al., 2003), DIPP in Finland (Hoppu et al., 2004), BABYDIAB in Germany (Hummel, Ziegler, & Roth, 2004), and ABIS (Stolt, Helgesson, Liss, Svensson, & Ludviggson, 2005) and DiPiS (Lernmark et al., 2004) in Sweden. The largest study of this type is the TEDDY study which will screen over 360,000 newborns to identify over 17,000 infants genetically at risk for T1D who will be invited into the study and followed for up to 15 years; it is expected that 7,800 genetically at-risk infants and their families will participate (TEDDY Study Group, 2007).

There is a small literature addressing the psychosocial impact of T1D genetic testing. Since testing is typically done in infants or very young children, this literature has focused primarily on parents, and usually mothers. Since ICA testing is often carried out in older children and adults, the psychosocial impact of ICA testing is included in this review. Study findings are organized by type of impact: cognitive, emotional, and behavioral.

Cognitive Impact of T1D Genetic and ICA Testing: Understanding T1D Risk

Studies examining the cognitive impact of T1D genetic or ICA testing have focused on participants' or family members' risk perception. If someone in the family has T1D, other family members seem to be well aware that the siblings or children of the T1D patient are at increased risk for the disease. Hendrieckx, DeSmer, Kristoffersen, and Bradley (2002) asked over 400 siblings and offspring of T1D patients to rate their own risk of developing T1D, compared to other people of their own age, on a five-point scale ranging from much lower to much higher; the mean score was 3.5, indicating that the study population was well aware of their own increased risk for T1D. Lernmark et al. (2004) asked parents of 12,000 infants genetically screened for T1D risk to rate their child's risk for T1D by selecting one of the four answers: no risk, don't know, small risk, or great risk. Parents in this study did not know their child's genetic test results. Most (63%) parents of infants with no first-degree T1D relative selected the "no risk" or "don't know" options. In contrast, parents of infants with a first-degree T1D relative were more likely to select the "small risk" (63%) or "great risk" (15%) answers. Although both of these studies document the fact that family members of T1D patients are well aware that siblings or offspring of the T1D patient are at increased risk for the disease, neither study informs us of what family members perceive the actual risk of T1D to be.

Actual lifetime risk of T1D in first-degree relatives of T1D patients varies across countries but is estimated to be 2–5% in the United States (Dorman et al., 1995). Among children who have the highest risk of T1D genotype and a first-degree relative with T1D, actual risk for the disease may be as high as 20–25% (Schatz et al., 2002). PANDA is one of the few genetic screening studies that provide parents with the child's actual risk for T1D at the time the parent is informed of the child's genetic test results. Parents of genetically at-risk babies are given both a label (e.g., high risk) and a numerical estimate (e.g., out of 100 babies like your

baby, 10 will go on to develop diabetes). Two studies interviewed mothers of genetically at-risk PANDA children about their child's T1D risk 1 and 4 months after risk notification (Carmichael et al., 2003; Hood, Johnson, Baughcum, She, & Schatz, 2006). Mothers' estimates of their child's T1D risk were compared to the child's actual risk and categorized into one of the four groups: accurate, risk underestimation, risk overestimation, or don't know. Both studies found that most mothers (73–79%) were accurate about their child's T1D risk at the 1-month interview but accuracy declined over time with more mothers (19–24%) underestimating the child's risk at the 4-month interview. In both studies, less educated mothers were less accurate. In addition, Hood et al. (2006) found that low maternal anxiety about the child's at-risk T1D genotype and high maternal depression were associated with risk underestimation. Johnson (2006a) reported the results of 1-year interviews with these same two cohorts of PANDA mothers. At 1 year, only half (48–49%) of these mothers were accurate about their child's T1D risk and the percentage of mothers who underestimated the child's risk increased to 34–35%. These mothers were interviewed again 3–4 years after learning their child was at increased risk for T1D. Accuracy further declined to 40%, and 42% were underestimating the child's actual risk (Baughcum, Johnson, She, & Schatz, 2008). These data from the PANDA studies suggest that while most mothers may accurately recall the child's risk soon after being informed of that risk, unless this risk information is repeated, many mothers underestimate the child's risk as time passes.

In contrast to the PANDA studies, Kerruish et al. (2007) found no decline in maternal risk perception accuracy over a 1-year time interval. The investigators asked mothers of genetically high-risk and low-risk infants to rate the child's T1D risk by selecting one of the following responses: no risk at all; less risk than most people; same risk as most people; higher risk than most people; will definitely develop diabetes; and uncertain. For the high-risk infants, "higher risk than most people" was considered an accurate response. For the low-risk infants, "less risk than most people" or "same risk as most people" was considered the accurate response. Most mothers were accurate when assessed at 1–2 weeks after risk notification and 1 year later and there was no evidence of underestimation except in the low-risk group where 7–8% of mothers thought their low-risk child had "no risk at all." There are a number of important differences between the Kerruish et al. (2007) study and the PANDA studies including country (New Zealand versus United States); number of mothers in the high-risk group ($N = 38$ in Kerruish et al.'s study, $N = 435$, 195, 192 in the PANDA studies); and different methods of determining risk perception accuracy or underestimation. There may also be important unspecified differences in how risk information was communicated across time to participating parents by the two sets of investigators; certainly repeating the information is likely to help maintain risk perception accuracy. One PANDA study tested the impact of sending a letter to home re-iterating the child's diabetes risk and found that it helped maintain risk perception accuracy over time (Carmichael, 2003).

Emotional Impact of T1D Genetic and ICA Testing: Anxiety, Worry, and Depression

Most studies have examined the emotional impact of ICA or T1D genetic testing, with anxiety and worry being the primary focus. A remarkable number of studies have used the state component of the State-Trait Anxiety Inventory (STAI) (Speilberger, 1973, 1983; Speilberger, Gorsuch, & Luchene, 1970) for this purpose. Table 1 summarizes the results of these investigations and provides STAI results for several comparison samples. Immediately after learning that you or a loved one is at risk for T1D, STAI scores are generally high, particularly among ICA-positive individuals and their family members (Hummel et al., 2004; Johnson et al., 1995; Johnson, Riley, Hansen, & Nurick, 1990). This is not surprising because an ICA-positive result indicates that pancreatic beta cell destruction is underway, substantially increasing the risk of T1D (see Figure 1). Some of the highest STAI scores reported are for mothers of ICA-positive children (Johnson et al., 1995; Hummel et al., 2004). STAI scores for parents of genetically at-risk children are substantially lower than scores of parents of ICA-positive children and appear to be influenced by parental role and whether the child has a first-degree relative with T1D. Mothers consistently report higher STAI scores than do fathers (Hummel et al., 2004; Johnson et al., 2007b; Simonen et al., 2006) and mothers and fathers report higher scores if the child has a first-degree relative with T1D than if the child does not (Johnson, Baughcum, Carmichael, She, & Schatz, 2004, 2007).

There also appear to be important country differences with Finland reporting lower STAI scores in both high-risk and low-risk samples (Johnson et al., 2007b; Simonen et al., 2006). Finland has the highest incidence of T1D in the world; since T1D is so common, it may be better known among the Finnish population and as a consequence, increased risk for the disease may be less anxiety provoking (Simonen et al., 2006). The results of the one study from New Zealand (Kerruish et al., 2007) are anomalous. Not only are the STAI scores reported very low but also there is a significant decline in STAI scores when parents learn that their child is at increased risk for T1D compared to parents in the comparison groups (parents of genetically low-risk infants and parents of infants who did not undergo genetic testing). This conflicts with Hummel et al.'s (2004) findings in which parents' anxiety increased when the parent learned that the child was at risk for T1D and declined when the parent learned that the child was not at risk. All parents in the Kerruish et al. (2007) investigation met with a physician who may have alleviated their concerns and since many of the study questionnaires were completed at the study visit, there may have been some pressure to report low anxiety subsequent to meeting with the physician. The STAI score was also given using "standard instructions." In other words, parents were asked not to think about their own child's T1D risk and complete the questionnaire (the approach used by many other investigators). This could explain the unusually low STAI scores. In fact when asked "how much do you think about your child's test

Table 1. STAI Scores of ICA-Positive Participants and Parents of ICA-Positive and Genetically At-risk Children Assessed at Different Times Pre- and Post-test Results

	Country	Pre-test	Post-test	4–6 Months Post-test	1 Year Post-test
ICA+ adults					
Johnson et al. (1990) ($n = 5$)	United States		52.2 ± 13.3	35.0 ± 10.1	
Johnson and Tercyak (1995) ($n = 34$)	United States		44.7 ± 12.7	34.1 ± 11.2	
ICA+ children					
Johnson et al. (1990) ($n = 18$)	United States		44.2 ± 7.3	33.2 ± 5.1	
Johnson and Tercyak (1995) ($n = 34$)	United States		41.9 ± 9.4	32.1 ± 6.6	
Mothers of ICA+ children					
Johnson and Tercyak (1995) ($n = 33$)	United States		55.4 ± 14.4	38.7 ± 8.7	
Hummel et al. (2004) ($n = 25$)	Germany	42.5 ± 10.4	51.3 ± 13.1		
Fathers of ICA+ children					
Hummel et al. (2004) ($n = 25$)	Germany	39.4 ± 7.6	43.8 ± 8.1		
Mothers of genetically at-risk children					
Johnson et al. (2004) ($n = 433$), Cohort 1	United States		37.0 ± 13.5	30.9 ± 11.0	28.1 ± 9.5
Carmichael (2003) ($n = 190$), Cohort 2	United States		36.1 ± 10.5	31.6 ± 10.5	29.8 ± 8.8
Simonen et al. (2006) ($n = 291$)	Finland		34.9 ± 11.4		

(Continued)

Table 1. *(Continued)*

	Country	Pre-test	Post-test	4–6 Months Post-test	1 Year Post-test
Kerruish et al. (2007) ($n = 38$)	New Zealand	31.1 ± 8.1	26.7 ± 5.8		29.6 ± 9.6
Johnson et al. (2007b)					
($n = 1,012$)	Finland		35.8 ± 8.8	32.0 ± 8.2	
($n = 270$)	Germany		38.1 ± 10.1	38.9 ± 10.4	
($n = 1,455$)	Sweden		39.9 ± 9.7	35.9 ± 9.1	
($n = 1,498$)	United States		41.2 ± 10.3	37.5 ± 10.7	
Baby has a first-degree T1D relative ($n = 468$)	All countries		41.1 ± 10.4	38.7 ± 9.7	
Baby has no first-degree T1D relative ($n = 3,773$)	All countries		39.0 ± 9.9	35.4 ± 9.8	
Fathers of genetically at-risk children					
Simonen et al. (2006) ($n = 272$)	Finland		32.1 ± 9.0		
Johnson et al. (2007b)					
($n = 896$)	Finland		33.5 ± 9.5	30.6 ± 8.5	
($n = 260$)	Germany		35.5 ± 10.1	37.0 ± 10.1	
($n = 1,283$)	Sweden		36.5 ± 9.6	33.0 ± 8.6	
($n = 1,254$)	United States		36.9 ± 10.2	34.8 ± 10.9	
Baby has no first-degree T1D relative ($n = 420$)	All countries		38.4 ± 10.2	36.9 ± 9.6	
Baby has no first-degree T1D relative ($n = 3,276$)	All countries		35.5 ± 9.8	32.9 ± 9.6	
Comparison groups					
Mothers of ICA– or genetically low-risk children					
Hummel et al. (2004) ICA– children ($n = 224$)	Germany	39.7 ± 10.3	37.1 ± 10.3		

(Continued)

Table 1. *(Continued)*

	Country	Pre-test	Post-test	4–6 Months Post-test	1 Year Post-test
Simonen et al. (2006) Genetically low-risk infants ($n = 290$)	Finland		33.9 ± 9.0		
Kerruisch et al. (2007) Genetically low-risk infants ($n = 76$)	New Zealand	33.6 ± 9.6	31.5 ± 8.3		30.1 ± 9.6
Fathers of ICA– or genetically low-risk children					
Hummel et al. (2004) ICA – children ($n = 189$)	Germany	37.8 ± 8.9	35.9 ± 8.1		
Simonen et al. (2006) Genetically low-risk infants ($n = 266$)	Finland		32.3 ± 8.9		
Other female comparison groups					
Mothers of newborns Kerruisch et al. (2007) ($n = 76$)	New Zealand	30.9 ± 7.8	30.4 ± 10.2		30.0 ± 9.6
Pregnant women undergoing amniocentesis Tercyak, Johnson, Roberts, and Cruz (2001) ($n = 100$)	United States	44.9 ± 11.0			
Pregnant women Marteau and Bekker (1992) ($n = 200$)	England	37.6 ± 11.0			
US working women Speilberger (1983) ($n = 210$)	United States	36.2 ± 11.0			

STAI, state component of State-Trait Anxiety Inventory; ICA+, positive for islet cell antibody; ICA–, negative for islet cell antibody. Data from comparison samples are also provided.

result" and "how much do you worry about your child's test result," mothers with high-risk infants in the Kerruish et al. (2007) study acknowledged that they thought about the child's test result and worried significantly more than did mothers of low-risk infants, findings consistent with the rest of the literature.

Table 1 also highlights the consistent decline in STAI scores over time (Carmichael, 2003; Johnson et al., 1995; Johnson et al., 1990, 2004, 2007b); only Kerruish et al. (2007) report different results. These data suggest that while at-risk individuals and parents of at-risk children may respond with elevated anxiety to the news that they or their child is at increased risk for T1D, as time passes this anxiety seems to dissipate.

However, the initial levels of anxiety and how quickly anxiety dissipates is a function of a number of variables that we are just beginning to understand. We know from the data presented in Table 1 that an ICA-positive test result induces more anxiety than does a positive genetic test result and parents of genetically at-risk children with a first-degree T1D relative report more anxiety than do parents of genetically at-risk children with no first-degree T1D relative. Both an ICA-positive test result and the presence of a first-degree T1D relative increase the actual risk of T1D which likely explains the associated heightened anxiety. We also know from Table 1 that mothers of at-risk children report more anxiety than do fathers, consistent with the larger psychological literature confirming higher reported levels of emotional distress in women than men (Gater et al., 1998; Piccinelli et al., 2000). Only a few studies have examined coping strategies employed by at-risk individuals or family members. It appears that most individuals rely on problem-focused coping and social support in response to their own or a loved one's increased T1D risk (Johnson et al., 2000; Johnson et al., 1990). However, certain coping styles – self-blame and avoidance – appear to be associated with heightened anxiety (Johnson et al., 2000; Simonen et al., 2006), although clearly more research is needed.

A few studies have examined parental depression in response to a child's positive T1D genetic test results. Anxiety and worry appear to be more common responses than is depression, although Simonen et al. (2006) reported that 30% of mothers and 12% of fathers reported depression in response to their child's high-risk T1D genetic test results. However, two studies that used standardized measures of depression did not find mothers of genetically at-risk infants to have elevated depression scores compared to normative samples (Hood et al., 2005; Kerruish et al., 2007). However, Hood et al. (2005) found that poorly educated, ethnic-minority mothers who suffered from either a history of major depression or post-partum depression were more likely to respond with depressive symptoms to the news of their child's increased risk for T1D. Certain coping styles (wishful thinking, self-blame, seeking social support) were also associated with increased depressive symptoms. It appears that most mothers respond effectively to the news of their child's increased T1D risk but a subset of mothers – those with a history of depression, who are poorly educated from ethnic-minority backgrounds, and who rely on certain coping styles – may be particularly vulnerable.

Although some investigators have been concerned that parents of genetically at-risk children would treat their children differently (Ross, 2003), there is almost no data that address this issue. Yu et al. (1999) found no increase in parenting stress associated with a positive genetic test results but only Kerruish et al. (2007) have attempted to assess parent attitudes toward the child using the Vulnerable Baby Scale (Kerruish, Settle, Campbell-Stokes, & Talyor, 2005). They found no evidence that mothers of at-risk infants viewed their infant as more vulnerable than comparison samples of parents with children with low genetic risk or parents of children that did not undergo genetic testing. However, the sample of high-risk children was small ($n = 38$), precluding any conclusion of "no effect" at this time. Simonen et al. (2006) reported that highly anxious parents were more likely to acknowledge "looking after their infant more carefully" after learning of the child's increased risk, suggesting that there may be a subset of parents who are more likely to view the child as particularly vulnerable and in need of special care and attention.

Behavioral Impact of T1D Genetic and ICA Testing: Surveillance and Disease Prevention

A number of studies have provided evidence that individuals who are at increased risk for T1D and the parents of at-risk children often engage in monitoring behaviors for possible T1D onset. As many as 80% of parents of children with T1D report blood glucose testing in unaffected siblings; in most cases they never report this type of surveillance to the child's physician (Lucidarme, Domingues-Muriel, Castro, Czernichow, & Levy-Marshall, 1998). Baughcum et al. (2005) conducted the most comprehensive study of parent behavior change in a sample of 192 at-risk PANDA children. Monitoring behaviors – blood glucose testing and watching for signs of diabetes – were reported by the majority of mothers interviewed. Many mothers also reported changing the child's diet or physical activity in an effort to prevent the disease. Lifestyle changes have been reported by a number of other investigators (Hendrieckx et al., 2002; Johnson et al., 1995) and were common in the Diabetes Prevention Trial for Type 1 Diabetes which targeted ICA-positive children and adults (Johnson et al., 2007a; Johnson, Baughcum, Rafkin-Mervis, & Schatz, 2009). These spontaneous efforts to prevent the disease are common despite the fact that there is no known means to prevent T1D (Simonen et al., 2006). Fortunately, potentially harmful prevention efforts (e.g., delaying the child's immunizations) appear relatively rare.

Reactions to Study Participation: Satisfaction and Burden

Studies of parents who have T1D themselves or who have a child with T1D report that >90% want their unaffected offspring tested for T1D risk (Hummel et al., 2004; Lucidarme et al., 1998). Parents of children with no family history of T1D may be less likely to seek T1D genetic testing but refusal of such testing when offered is relatively uncommon and most participating parents report that they feel it is good to know about the child's

risk, despite the fact that there is no prevention available (Helgesson et al., 2008; Simonen et al., 2006; Stolt, Liss, & Ludvigsson, 2003; Swartling, Eriksson, Ludvigsson, & Helgesson, 2007). However, it is likely that there are important country and cultural differences in parents' willingness to subject their child to genetic testing and their reactions to test results, particularly in populations with no family history of T1D. Certainly the invasiveness of the screening procedure is likely to be important. Genetic screening done at birth, requiring no extra needle stick, is likely to be far more acceptable than drawing blood from an older child. Hummel et al. (2004) noted that the blood draw was distressing for the child and regular blood draws required by the TEDDY protocol is one of the primary reasons parents of genetically at-risk infants decline to join the TEDDY study (Johnson, 2006b). Since T1D genetic testing and ICA screening are conducted only as part of research protocols, at-risk participants are often asked to join natural history or prevention studies that can be very demanding. Only recently have investigators begun to examine the extent and nature of participant burden in these trials. When asked, children often view blood draws and other invasive procedures as more distressing than do their parents or at-risk adult trial participants (Johnson et al., 2007a, 2009). However, once parents or children join a study, they usually report high satisfaction with the study. They are reassured by the close monitoring the study provides and are often optimistic that an experimental intervention will succeed (Johnson et al., 2007a, 2009; Tercyak, Johnson, & Schatz, 1998).

IMPLICATIONS FOR PATIENT CARE, RESEARCH, AND HEALTH POLICY

Although genetic testing for T1D risk remains in the formative stage, the available scientific literature is relevant to current patient care, future research, and health policy.

Patient Care

It appears that parents who have T1D themselves or have a child with T1D may seek T1D genetic testing for their unaffected offspring. Consequently, physicians need to be prepared to address this issue. Since there is currently no known means of preventing T1D in genetically at-risk individuals, it is best to refer interested families to research centers where such genetic testing is conducted in clinical studies with appropriate Institutional Review Board oversight. These research centers will have the most up-to-date information on genetic testing and can provide families who wish to participate with the most accurate assessment of risk as well as information about available natural history studies or prevention trials. Given the uncertainty of the impact of a high-risk T1D genetic test result on a US child's future insurability in the US health-care sector, the family should consider keeping such results out of the child's

medical record. This is not a concern in other countries that offer universal health care.

Our research findings to date also suggest that risk communication is a difficult task, even in research centers with a great deal of experience with T1D genetic testing. Although most participants seem to understand their own or a child's risk soon after risk notification, there remains a substantial minority who do not and over time, the number of people who have inaccurate risk perceptions seems to increase. Research centers need to carefully monitor families' understanding of risk to assure that the center's effort to explain risk has been successfully communicated. Studies by Stolt et al. (2005) and Swartling and Helgesson (2008) have highlighted the disconnect between parents' self-reported understanding of a study protocol and the accuracy of their recall; parents often believe that they have an accurate understanding of a study's purpose or procedures when their actual knowledge is inaccurate. These studies' findings strongly suggest that simply asking families whether they understand the genetic risk information provided will be insufficient. Research centers that do T1D genetic testing will need to conduct much more detailed assessments of families' risk perception accuracy if they are to assure accurate communication of genetic risk information.

The available scientific literature suggests that most people cope well with the news of their own or a family member's increased risk for T1D. However, there are certain populations that may be particularly vulnerable to high levels of anxiety that do not dissipate over time or to depression. These include parents of ICA-positive children and parents of a genetically at-risk child who has an immediate family member with T1D; mothers, in particular, can be especially worried or anxious. Since families with a history of T1D are most likely to seek T1D genetic testing, the potential psychological needs of these individuals need to be given careful consideration. Individuals with a history of depression, including post-partum depression, may be particularly vulnerable to depressive symptoms in response to the news that their child is at risk for T1D. Certain coping styles – self-blame and avoidance – also seem to be associated with poorer psychological resilience. Research centers that do T1D genetic testing need to be sensitive to the psychological impact of such testing and provide psycho-educational support and resources to those in need.

Future Research

There are many research questions of interest but a few deserve our particular attention. Since most "genetic" diseases are not associated with 100% risk of developing the disease, the need to devise successful ways to communicate relative risk of a disease to families remains extremely important. Risk communication that is meaningful for children, or for adults with low levels of education, is particularly challenging. This research is critical not only for T1D genetic testing but also for genetic testing with children in general.

We know something about those subpopulations that may be particularly vulnerable to high levels of anxiety or depression in response to a

high-risk T1D genetic test result. However, in addition to developing effective screening programs to identify potentially vulnerable family members, we have yet to develop successful intervention strategies to help families cope effectively with the possibility that a family member may develop T1D.

We know almost nothing about family members' treatment of a child who is at increased risk for T1D. We do know that families often monitor the child closely for possible T1D onset but the impact of this additional surveillance on the child's psychosocial development remains unknown. It appears that family members' efforts to prevent T1D are not generally harmful but very few studies have examined possible over-protective parenting behaviors. We have no a priori reason to suspect that T1D genetic testing would be psychologically harmful to the child but some have certainly raised this possibility and research that addresses this issue with objective scientific data would be welcome.

Most T1D genetic testing studies are conducted in infants and young children. As these children mature, parents must face the decision of when and how to tell a child of his or her increased T1D risk. We have yet to conduct the necessary research to give parents evidence-based guidance in how best to approach this responsibility.

T1D genetic testing is likely to be associated with natural history or prevention trials that raise a host of additional psychosocial research questions. Is psychological stress an environmental trigger for T1D? How much consideration should investigators give to children's, versus their parents', reactions to invasive study procedures; should children who do not want to be in a trial be included if their parents insist on their participation? How do families' efforts to prevent T1D impact prevention trial design and interpretation? Can study dropouts be identified at the beginning of a prevention or natural history study, and if so, can this dropout be minimized by particular strategies or interventions? These are just a few of the interesting questions posed by this type of research, questions that can best be answered by assuring that behavioral scientists are included in T1D trials' investigator teams.

Health Policy

Health policy issues relevant to T1D genetic testing are those that are relevant to genetic testing in general. These include the possible exclusion from health insurance in the United States of persons who have undergone such testing with a positive result; the concern is that US insurance companies will argue that such individuals have a "pre-existing" condition and refuse coverage. Congressional legislation may ultimately preclude such discrimination in the United States and this is not a problem in countries with universal health care. However, all health organizations will need to determine when and if genetic testing for T1D (or any other disease) risk is part of health coverage and if genetic counseling and psychological services associated with high-risk results are included. Similarly, will the cost of prevention in genetically at-risk individuals be covered and if so, which prevention options will be included and which will be considered "experimental" and excluded? In any system with finite health-care dollars, there

will always be tension between the cost of assuring that people with the disease receive adequate treatment and the cost of preventing the disease in currently unaffected but "at-risk" individuals.

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13

Cardiovascular Disease Risk

SUMA POTINY and SARAH CLAUSS

INTRODUCTION

The precise genetic mutations that directly cause or play some role in coronary artery disease (CAD), cardiomyopathies, cardiac arrhythmias, and pulmonary artery hypertension have begun to be identified. The majority of the genetic mutations of hypertrophic and dilated cardiomyopathies have also been described. Many of the genes responsible for cardiac arrhythmias, such as long QT syndrome, have been identified as well. In this chapter, we will specifically address the genetics of CAD, hyperlipidemias, obesity, and other transmitted cardiovascular risks from parent to child. We will review the complex interaction of genetics and the environment that predispose families and children to cardiovascular disease and the implications for health and disease prevention. The understanding of the genetic basis of CAD and the interaction between genes and the environment may improve our prevention, treatment, and care of the sequelae of CAD.

BACKGROUND AND SIGNIFICANCE: ATHEROSCLEROSIS AND ITS RISK FACTORS: THE PRECURSORS TO CAD

Cardiovascular disease is the leading cause of death in the United States. In 2005, CAD and stroke caused 869,700 deaths (American Heart Association, 2008). Further, 13 million people in the United States alone are affected by a complication of cardiovascular disease. Cardiovascular disease is influenced by both environmental and genetic factors, and much of the morbidity and mortality associated with CAD may be preventable. As early as 1958, the Framingham study published risk factors for coronary heart disease that included smoking, hypertension,

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hyperlipidemia, obesity, and diabetes (Dawber, Moore, & Mann, 1957). There is also increasing evidence that many of these risk factors may have a heritable component and cluster in families. Intervening earlier, to identify high-risk groups, decreased risky behaviors and increased healthy behaviors are critical to decreasing the consequences from this devastating illness.

Autopsy studies from the Pathological Determinants of Atherosclerosis in Youth (PDAY) study and Bogalusa Heart Study have shown that the atherosclerotic disease process begins in childhood (Berenson et al., 1998; McGill, McMahan, Malcom, Oalmann, & Strong, 1997; McGill et al., 2001; Newman et al., 1986). The PDAY study examined the relation of risk factors to the presence of arterial fatty streaks and fibrous plaques in individuals aged 15–34 who died from suicide, homicides, or by accident (McGill et al., 1997, 2001). This study showed that preclinical vascular changes (fatty streaks and fibrous plaques) were associated with increased cholesterol and elevated blood pressure. Other studies showed that decreased high-density lipoprotein (HDL) cholesterol concentrations, increased non-HDL cholesterol concentrations, hypertension, obesity, hyperglycemia, and smoking are significant risk factors and are associated with increased atherosclerosis (McGill & McMahan, 2003; McGill et al., 2000; Solberg & Strong, 1983).

Carotid intima–media thickness (CIMT) has been used to correlate risk factors with the risk for CAD. Increased thickness of the intima–media layers of the carotids is a measure of preclinical atherosclerosis and is used to determine the risk of cardiovascular disease. Specifically, increased carotid intima–media thickness has been associated with increased likelihood of stroke, myocardial infarction (MI), and coronary artery disease in adults (Pearte et al., 2006; Van der Meer et al., 2004). The Young Finns Study showed that increased childhood LDL concentrations, systolic hypertension, smoking and obesity in childhood were significantly associated with increased CIMT (Raitakari et al., 2003). Using CIMT measurements in children, studies have found that children with elevated serum cholesterol levels due to familial hyperlipidemia (FH), with hypertension, and with obesity all have increased CIMT compared to controls and therefore may have an increased risk of future MIs and stroke (Iannuzzi et al., 2004; Litwin et al., 2004; Pauciullo et al., 1994).

There is evidence that not only are coronary artery risk factors present in childhood but that risk factor assessment at a young age is actually more predictive of coronary heart disease risk in adulthood than is screening for risk factors in adulthood. The CARDIA study followed young subjects (<20 years) over the course of 15 years. Risk factors (smoking, cholesterol levels, hyperglycemia, hypertension, and obesity) for CAD were assessed at years 0, 5, 10, and 15. Coronary artery calcium (CAC) was measured at the 15-year mark. CAC is directly related to atherosclerotic plaque and has been shown to be associated with coronary risk factors (Breen et al., 1992; Margolis et al., 1980; Mautner et al., 1994). The odds ratio that the risk factor assessment at year 0 would be predictive of CAC was 1.14 (95% CI 1.10–1.19) and 1.09 at

year 15 (95% CI 1.06–1.12). This study implies that early screening and intervention is important in preventing cardiovascular disease later in life.

GENETICS OF LIPID METABOLISM

In addition to the previously noted risk factors, it is apparent that there is a strong heritable component to coronary artery disease. Both family and twin studies validate this observation. In a study of 21,000+ Swedish twins, the relative risk of MI was obtained after one twin died from an MI (Marenberg, Risch, Berkman, Floderus, & de Faire, 1994). When a male twin died from an MI, the hazard ratio that the other twin would subsequently suffer an MI over a 26-year period was 8.1 (95% CI 2.7–24.5) for monozygotic twins and 3.8 (95% CI 1.4–10.5) for dizygotic twins. For females, if one female twin died before the age of 65 from coronary artery disease, the hazard ratio of MI was 15 (95% CI 7.1–31.5) in monozygotic twins and 2.6 (95% CI) for dizygotic twins. In this study, this risk decreased (risk ratios approached 1) if the MI in the twin occurred at an older age, indicating that a genetic contribution confers coronary artery disease at younger ages (younger than 55 in men and 65 in women) (Slack & Evans, 1966).

Although the genetic contribution to the development of coronary artery disease is challenging to elucidate, there are some syndromes that follow a Mendelian pattern of inheritance, where a single-gene locus aberration affects cholesterol and results in hyperlipidemia and premature CAD.

Familial hypercholesterolemia (FH) is caused by a defect in the LDL receptor which results in impairment in the removal of LDL particles from the circulation. More than 900 mutations in the LDL receptor gene locus have been identified that can lead to disease (Cambien & Tiret, 2007). One in 500 people is heterozygous for the mutation, and one in 1 million is homozygous for the mutation. Heterozygotes will have average levels of total cholesterol (TC) and LDL cholesterol of 300 and 240 mg/dl, respectively, and homozygotes will have 600–1,000 and 450–850 mg/dl, respectively. Homozygous individuals have severe atherosclerosis and often have MI in childhood.

Familial defective apolipoprotein B-100 is caused by a substitution of adenine for guanine in exon 26 of the apolipoprotein B gene (Defesche, Pricker, Hayden, van der Ende, & Kastelein, 1993; Tybjaerg-Hansen & Humphries, 1992). The substitution results in a mutation at amino acid 3,500 and results in decreased affinity of LDL to the LDL receptor. This, in turn, leads to an increase in levels of plasma LDL cholesterol. One in 1,000 people are heterozygous for this mutation, and their lipid profiles are similar to those with LDL receptor mutations.

Autosomal recessive hypercholesterolemia (ARH) is an extremely rare genetic mutation that has a similar phenotype to homozygous familial hyperlipidemia (with the exception that parents of those with ARH will have a normal lipoprotein profile). This disease is caused by a defect in

a hepatic protein which then results in the failure of clearance of plasma LDL. Patients with ARH have mutations in the LDL receptor adaptor protein (LDLRAP1), which is an adaptor protein that is necessary for the interaction between the LDL particle and the cytoplasm (Eden et al., 2002). The genetic mutation was isolated by Garcia et al. (2001) on chromosome 1 in 2001.

Tangier disease is a rare, autosomal recessive disorder. People with this disorder store cholesterol esters in peripheral nerves, lymphatic tissue, bone marrow, and in the reticuloendothelial cells in the liver and spleen. The HDL values in these patients are close to zero. The molecular defect is due to a mutation in the ABC transporter protein named ABCA1 (Bodzioch, Orso, & Klucken, 1999; Brooks-Wilson, Marcil, Clee, & Zhang, 1999; Rust et al., 1999).

Sitosterolemia is also a rare disorder and is due to genetic mutations in the *ABCG5* and *ABCG8* genes, both of which are found on chromosome 2p21 (Berge et al., 2000). The products of these genes are transporter proteins that export cholesterol into the lumen of the intestine, thereby decreasing GI absorption of cholesterol from the diet. These proteins also regulate liver cholesterol synthesis. Thus, an individual with this mutation absorbs almost all dietary fats and cholesterol, and may achieve better disease control with a strict diet. These patients have a wide range of cholesterol levels, from high normal to very high (150–650 mg/dl).

An autosomal dominant form of hypercholesterolemia caused by a mutation of the proprotein convertase subtilisin/kexin-type 9 (*PCSK9*) gene leads to a similar clinical presentation as heterozygous FH (Abifadel et al., 2003). One specific mutation, Asp375Tyr, is found in families with Norwegian and English descent. The mechanism by which *PCSK9* causes hypercholesterolemia is not yet fully understood but is known to be involved in cholesterol transport (Maxwell & Breslow, 2004; Park, Moon, & Horton, 2004).

The disorders described above are monogenic, whereas many other diseases are polygenic and/or may be more susceptible to gene–gene and gene–environmental interactions. For example, individuals with familial combined hyperlipidemia (FCHL) have variable disease expression. The typical abnormalities in lipoproteins are elevated LDL, triglycerides, and low HDL. However, these patients may have a combination of obesity, hypertension, hyperinsulinism, and glucose intolerance. Because different patients have different phenotypic expressions of the disease, it makes sense that this disease is under the influence of a number of different genes. One of these genes is upstream transcription factor-1 (*USF-1*) gene described by Pajukanta et al. (2004).

Another example of a polygenic disease is familial hypertriglyceridemia. This is typically not expressed fully until adulthood. The plasma levels may be only somewhat elevated in childhood and then become extremely elevated in adulthood. The susceptibility to hypertriglyceridemia is found on several genetic loci and is associated with mutations in the lipoprotein lipase, hepatic lipase, apolipoprotein A5 (*APOA5*) gene, and the lipase I (*LIPI*) gene (Ruel, Couture, Cohn, & Lamarche, 2005).

Patients with familial hypoalphalipoproteinemia A have low levels of HDL cholesterol. The etiology of this disease is heterogeneous as well. To date, it has been mapped to mutations in the *ABC1* gene on chromosome 9 and in others to mutations in apolipoprotein A (*APOA1*) gene on 11q23.3 (Law, Gray, Brewer, Sakaguchi, & Naylor, 1984; Luciani, Denizot, Savary, Mattei, & Chimini, 1994). There are many more polymorphisms that result in abnormalities in the *APOA1* complex causing low HDL (including familial HDL deficiency) which may or may not lead to premature CAD (Funke et al., 1991; Gualandri et al., 1985; Utermann et al., 1982; von Eckardstein et al., 1989).

In summary, specific genetic alterations leading to coronary artery disease with a clear pattern of inheritance have been identified, but are relatively rare, and comprise a small portion of the population that develops coronary artery disease. The genetic basis of "common" atherosclerotic disease and MI (non-Mendelian disorders) still remains largely unknown. However, as genomic resources expand, we will have greater successes at identifying these genes. Given the early results and no unifying chromosomal abnormality at this time, cardiovascular disease is clearly heterogeneous with variable gene–gene and gene–environmental interactions.

OBESITY AND THE RISK FOR HEART DISEASE

Obesity has a genetic basis, however, as with coronary artery disease; the occurrence of obesity is usually the result of complex interactions between genes and environment. The current evidence that supports the strong heritability of obesity includes concordant twin studies, familial clustering, monogenic forms of obesity, and syndromic obesity. Genes for obesity do exist and their characterization is underway. Nearly 200 cases of human obesity had been identified and associated with a single-gene mutation in 11 different genes (http://obesitygene.pbrc.edu) (Rankinen et al., 2006). Polygenic obesity is based on the analysis of single-nucleotide polymorphisms (SNPs) and many candidate-gene and genome-wide linkage studies are underway. Genetic factors in obesity are detailed in another chapter of this volume; in this section, we review the epidemiology and risk of obesity and cardiovascular disease.

Obesity is a growing epidemic among children. According to the National Center for Health Statistics study in 1999–2002, approximately 16% of American children between the ages of 6 and 19 are obese [body mass index (BMI) $\geq$95%], which is a 45% increase from 1988 to 1994 (Hedley et al., 2004). Obesity has been noted to be a risk factor for cardiac disease in adulthood, leading to left ventricular dilatation as well as coronary artery disease risk factors (such as hyperlipidemia, diabetes, and hypertension) (Haji et al., 2006). Subjects from this same cohort were cross-sectionally analyzed to establish the presence of risk factors in obese children. Among 10,000+ subjects aged 5–17 years who had BMI >95%,

39% had at least two risk factors for coronary artery disease (hyperlipidemia, elevated blood pressure, and elevated insulin levels). Among those children who had a BMI >99%, 59% had at least two risk factors for coronary artery disease (Freedman, Mei, Srinivasan, Berenson, & Dietz, 2007).

Obesity is associated with not only an increased rate of coronary artery disease risk factors but also earlier occurrence of acute coronary events. In a study of 906 adult patients admitted to the hospital after an acute MI, obese patients were on average 8.2 years younger (p <0.001, CI 6.2–10.1) than normal weight controls (Suwaidi et al., 2001). Therefore, obese individuals have increased risk factors for CAD and may develop clinical events earlier possibly, resulting in an increase in morbidity and mortality over their lifetime.

Studies have also demonstrated that obese children often grow up to become obese adults. The Bogalusa Heart Study, which followed a cohort of 2,617 Americans older than 17 years (the first examination in childhood from ages 2 to 17 years), found that of children with a BMI ≥99%, 88% remained morbidly obese in adulthood (BMI ≥35) (Freedman et al., 2007). Thus, identification and treatment of obesity in childhood are critical to the prevention of coronary heart disease in adults.

Obesity is known to cause endothelial dysfunction (ED). ED is caused by oxidative stresses and is associated with development and progression of atherosclerosis and CAD. A study by Woo et al. examined 36 overweight children (mean BMI = 25) compared to non-obese children (BMI <23) (Woo et al., 2004). The authors showed that overweight and/or obesity independently correlated with abnormal endothelial function. Therefore, some children with obesity have increased risk factors for CAD and have impaired endothelial function which may increase their likelihood of cardiovascular disease.

Twin and parent–offspring studies also demonstrated that obesity has a strong genetic component. A review article published in 1997 performed an analysis of twin, adoption, and family studies (Maes, Neale, & Eaves, 1997). The mean BMI correlation was found to be 0.74 for monozygotic twins, 0.32 for dizygotic twins, 0.25 for siblings, 0.19 for parent–offspring, and 0.06 for adoptive relatives. In a family study by the Framingham group, heritability of mean BMI was 0.37, and maximum BMI 0.4, indicating further support that obesity has a genetic component (Coady et al., 2002). In a study that incorporated 53 pairs of monozygotic twins reared apart (negating the effects of a shared environment), the BMI correlation was 0.79 (Allison et al., 1996). These findings suggest that genetics has a stronger impact on the BMI of a person than does environment alone.

Verifying the role of obesity genes is still challenging in settings in which environmental factors may have a strong impact. Given that obesity is a large health problem that leads to significant morbidity and mortality, including cardiovascular disease, it is no surprise that this has been an active area of research, particularly in the field of genetics. As genetic research progresses and identifies different genomic alterations implicated in obesity, it is important to take into consideration the gene–environment relationship implicit in obesity and cardiovascular disease risk.

ENVIRONMENTAL FACTORS OF CARDIOVASCULAR DISEASE RISK

Environmental factors impact and modify genetic susceptibilities. Currently, schoolchildren have decreased physical education, increased consumption of foods high in saturated fats and simple sugars, increased portion sizes, and persistent use of tobacco. These factors have resulted in increased risk of cardiovascular disease. Each of these environmental factors is reviewed below.

Participation in Physical Activity

Sedentary behavior in our youth has increased as a result of multiple factors, including the increased use of automotive transportation (cars/buses/elevators/escalators, etc.), decreased outdoor play, and increased television/computer use (including video games). The Youth Risk Behavior Surveillance (YRBS) study in 2007 showed that only 30% of students have daily physical education class and only 37% of students achieve the recommended 60 min of exercise daily (Eaton et al., 2007). Between 1991 and 2003, there was a 13% decrease in enrollment in daily physical education in high school students (Centers for Disease Control and Prevention, 2004). Children are also involved in less physical activity while at home. Eaton et al. found that 35% of children watch at least 3 h of television per day (Eaton et al., 2007). Some parents also perceive their neighborhood as unsafe for their children to play in and therefore are more likely to keep their children indoors – resulting in more sedentary behaviors (Lumeng, Appugliese, Cabral, Bradley, & Zuckerman, 2006). With the decrease in physical activity opportunities at school and the perceived and real barriers at home, less than one-half of our children are not attaining adequate daily activity.

Dietary Trends

Television is used to market foods that are higher in saturated fats and simple sugars. For example, studies have shown that children are biased after only 30 s of a commercial and may be more likely to chose those foods that are nutrient poor and calorically high (Batada & Wootan, 2007). Furthermore, there is a significant correlation between watching television and eating and snacking when not hungry (Epstein, Saelens, Myers, & Vito, 1997). Therefore, a significant proportion of children are watching more television, making poorer dietary choices and eating out of habit instead of hunger. These trends are positively associated with obesity and an increased risk of cardiovascular disease over time (Giammatei, Blix, Marshak, Wollitzer, & Pettitt, 2003).

Changes in the diets of children and adolescents also correspond to increased portion sizes, increased consumption of saturated fats and simple sugars, and reduced intake of fruits and vegetables (Cavadini, Siega-Riz, & Popkin, 2000; Nielsen, Siega-Riz, & Popkin, 2002; Wright,

Wang, Kennedy-Stephenson, & Ervin, 2003). Snacking has increased, contributing up to 25% of daily energy intake in children (Jahns, Siega-Riz, & Popkin, 2001). Data from the Dietary Intervention Study in Children (DISC) showed that snacks, desserts, and pizza accounted for about one-third of daily intake in the adolescents they studied (Van Horn, Obarzanek, Friedman, Gernhofer, & Barton, 2005). Snack foods and desserts are often high in refined carbohydrates, salt, sucrose/fructose, and hydrogenated shortening, which provides a high glycemic index, resulting in obesity, increased low-density lipoproteins, and insulin resistance that may result in the development of obesity and type 2 diabetes (Kerver, Yang, Bianchi, & Song, 2003; Ludwig, 2002; Ludwig & Ebbeling, 2001; Ludwig et al., 1999; Pereira et al., 2002). In summary, these data are troubling in that there is a decreasing trend in healthful eating behaviors among youth, and the food choices they do make are implicated in increased cardiovascular disease risk.

Ethnic and cultural variations affect eating habits as well. African-American boys have a higher daily percentage of fat intake as compared to other ethnicities. Indicators of insulin resistance (i.e., pre-diabetes) were more prevalent in African-American children and children of Mexican descent relative to children who are white (Winkleby, Robinson, Sundquist, & Kraemer, 1999). Eating practices amongst consecutive generations of immigrants have also been shown to change over time. For example, first-generation Asian and Latino adolescents consume more fruits and vegetables and less sodas than do white adolescents. However, with each successive generation, the Asian diet remains stable, while the Latino diet shows an increase in soda consumption and decrease in the general nutritional content of food (Allen et al., 2007). Thus, cultural patterns of food consumption vary by ethnic group, differ by country of origin, and may change with each progressive generation within the United States.

Ethnicity and cultural tendencies toward cardiovascular disease are also affected by the environment, as population migration studies have shown. For example, individuals who live in Japan have a much lower incidence of coronary artery disease than do individuals living in the United States, but individuals from Japan who immigrate to the United States and adopt a more Western lifestyle tend to have the same incidence of coronary artery disease as other Americans (Lusis, Mar, & Pajukanta, 2004). Consequently, the development of cardiovascular disease is subject to not only genetic alterations but also their degree of expression within an individual and the individual's specific interactions with the environment.

There is an emerging literature citing stress as an emerging risk factor for obesity. Stress has a direct effect on the hypothalamic–pituitary–adrenal axis, resulting in increased plasma cortisol which is thought to be associated with the development of obesity (Lupien, King, Meany, & McEwen, 2000). The precise relationship between stress, race/ethnicity, and the development of obesity is not yet fully understood.

Tobacco Use

An additional public health issue is the prevalence of tobacco use among youth. The majority of smokers begin smoking before the age of 18 years. The most recent YRBS data showed that 20% of students surveyed had smoked a cigarette during the last month (Eaton et al., 2007). Cigarette smoking has decreased among adolescents between 1997 and 2002; however, the overall rates of tobacco use since that time has not changed substantially (Centers for Disease Control [CDC], 2003, 2006; Johnston, O'Malley, Bachman, & Schulenberg, 2007). One positive trend has been that the rate of cigarette smoking among female and Asian students has declined (CDC, 2007). Reduction of the use of tobacco products is a national health objective; however, these statistics make it clear that tobacco use continues to be a problem and is a significant risk factor for cardiovascular disease.

CHILDREN/ADOLESCENT/FAMILY SOCIAL, PSYCHOLOGICAL, AND BEHAVIORAL ISSUES

A recent statement endorsed by the American Academy of Pediatrics and the American Heart Association summarizes the current recommendations for lipid screening and treatment, the details of which are beyond the scope of this chapter (Daniels, Greer, & the Committee on Nutrition, 2008; McCrindle et al., 2007). Current diagnostic strategies include detailed family history (for cardiovascular disease, obesity, hypertension, dyslipidemia, and cigarette smoking), a fasting lipid profile screening of children $\geq$2 years if there is a positive family history for the above-mentioned risk factors, and a thorough evaluation of dietary history and physical activity levels. At present, genetic testing is not used to diagnose pediatric hyperlipidemia.

Identifying young patients with abnormal cholesterol levels allows the medical community to initiate diet and lifestyle modifications and/or medications as necessary. However, there are some concerns that this early intervention may also have negative consequences, for example, concern regarding future cardiac events may result in anxiety, depression, and strained family relationships. To date, this concern has yet to be realized – as studies among those with familial hyperlipidemia (FH) have not shown significant harmful effects on their psychological well-being (deJongh et al., 2003; Michie, Bobow, & Marteau, 2001; Tonstad, Novik, & Vandvik, 1996).

For example, de Jongh et al. noted that there were no problems related to quality of life or anxiety in children with FH treated with statins (deJongh et al., 2003). However, one-third of children with FH thought that their condition might be cured, and >40% thought that they suffered from the disease and its treatment. Thirty-eight percent of parents thought that FH was a burden and 79% felt that they suffered

because their child had FH (deJongh et al., 2003). These statistics reinforce the need for ongoing education and counseling of patients and families. Tonstad et al. conducted a study in Norway evaluating 86 girls and 66 boys in a lipid clinic (Tonstad et al., 1996). Twenty-five percent had lost a parent due to cardiovascular sequelae of FH. The majority of the children had similar psychosocial profiles relative to the general population. Children whose parents had cardiovascular sequelae had a lower Global Assessment Score. Of all the patients, only a few children had social or emotional problems, family conflict, or difficulties adhering to dietary recommendations or medication (Tonstad et al., 1996). The family dynamics and the development of the child are affected by the FH diagnosis, and it is important to treat not only the patient but the entire family as the disease is present in all aspects of their global environment.

Adherence to diet/lifestyle/medication is influenced by the family, by the peer group, as well as by the patient (Kools, Kennedy, Engler, & Engler, 2008). Each family is unique in how they respond to the diagnosis, act as role models, determine food availability/eating patterns at home, and maintain the family diet. Each individual patient has his/her own level and rate of development of understanding the disease, perception of the diagnosis, and individual dietary practices. Furthermore, peers and the social framework in which the patient and family operate influence meals/snacks and concerns about fitting into peer groups and school environments.

Rosenthal et al. have shown that those who are successful in achieving dietary modifications often have a cohesive family with low conflict (Rosenthal, Knauer-Black, Stahl, Catalanotto, & Sprecher, 1993). Burke, Dunbar-Jacobs, and Hill (1997) have shown that knowledge and understanding of the disease result in better success of diet and lifestyle modifications. Other authors have shown that specific, real-life dietary and social problem-solving skills and involvement in family meal planning need to be targeted and reinforced (Hanna, Ewart, & Kwiterovich, 1990; Mackner, McGrath, & Stark, 2001). Frequent, specific and detailed teachings may help patients and families understand the disease process and implications, and help them accomplish diet and lifestyle modifications.

CONCLUSIONS

Genomic science has come to the forefront of medical care. For some diseases, we have precise tests to detect alterations responsible for specific diseases. Several genetic tests have the potential and the capability to extend beyond simple detection of mutations or diagnoses of a disease; these have the ability to test prior to the onset of symptoms or to test genotype-specific responses to drug therapy (Robin, Tabereaux, Benza, & Korf, 2007). Therefore, asymptomatic patients may undergo testing for a genetic disease which they have a risk for, possibly leading to earlier diagnosis and treatment. Further genetic tests may be able to help guide specific therapies (i.e., inflammatory biomarkers and warfarin-specific dosing to genotype).

The role of genetic testing for clinicians, physicians, and scientists is evolving. Results may reveal information of unknown significance, and one cannot necessarily forecast how genes may be modified within the environment and how the disease will be expressed. Finally, genetic testing may have other ramifications, posing ethical, legal, and social questions. Genetic testing may result in internal conflict within an individual or a family unit that may lead to feelings of discrimination and anxiety. Social welfare and individual rights have already begun to be debated within the judicial system. Cardiovascular risks must be considered in this light as well.

Genetic testing is currently used to diagnose some disorders. In the future, genetic testing for those at risk for a disorder may be helpful to prevent or delay the onset of disease. The field of pharmacology will continue to evolve as we learn how distinct genotypes respond differently to different drugs and will offer more specific drug therapies.

The studies outlined in this chapter show how much we have learned about the genetics of cardiovascular disease. Clearly, there is much more to be identified. There are some single-gene disorders, but the remainder (and those leading to the majority of heart diseases) are quite complex, typically polygenic in etiology and have environmental modifiers. Today, the majority of cardiac diseases are diagnosed through history, physical exams, and specific testing (echocardiogram, plasma/serum analysis). It is clear from the available research that we stand at the precipice of a new era of medicine and that the future of diagnosis and management of cardiovascular disease will continue to evolve with genetics playing a key role in this process.

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14

Obesity Risk

SASKIA C. SANDERSON and MYLES S. FAITH

INTRODUCTION

Obesity rates in adults and children have risen at alarming rates over the past three decades, with one in three adults in the United States being obese and almost one in five children being overweight (Hedley et al., 2004). It has been projected that, for the first time, this generation of children will die at a younger age than their parents (Olshansky et al., 2005). The obesity epidemic has most certainly been fueled by changes in the environments in which people live, primarily in the increase of sedentary jobs, lifestyles and leisure activities, and the easy access to and availability of inexpensive energy-dense foods and drinks. These environmental changes over the past two decades have led many to dismiss the role of genetics as contributing to childhood obesity onset and the current obesity epidemic. However, as noted below, there is compelling evidence that family history and genetics are critical to the onset of childhood obesity; moreover, certain children may be more susceptible or responsive to the "obesogenic" environments in ways that put them at increased risk to gain excess body fat during growth.

There is strong evidence to suggest that genetic factors play a role in the development of obesity. While much of the scientific community is focused on genes involved in metabolism and physiological processes related to obesity onset, the influence of genes on food preferences, binge eating, emotional overeating, and other eating traits has been relatively underexplored. In this chapter, we review the evidence for genetic influences on obesity-related eating traits. The chapter focuses on eating traits through which obesity-predisposing genes become expressed and how these issues are studied in developing children. The chapter begins with a brief review of the concept of energy balance, noting that daily energy imbalances as slight as 30 cal/day, in young children, can lead to obesity onset. Next, the chapter reviews the strong evidence for familial transmission, and inheritance (or "heritability"), of obesity. The following section

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addresses the issue of obesity-promoting eating behaviors, arguing that certain eating patterns and food preferences that contribute to obesity onset may be heritable – just like metabolic or physiological processes. The chapter then reviews the "high-risk" research design as a strategy to investigate the development of body fat and eating behaviors in children predisposed to obesity. Data from the University of Pennsylvania's "Infant Growth Study" and the United Kingdom's "Twins Early Development Study" are presented. Next, commentary is provided regarding specific genes that confer risk for obesity, with attention to the *FTO* gene. The construct of emotional eating is then reviewed, followed by a discussion of genetic testing for obesity. The chapter concludes by discussing topics for future research, including implications of genetics studies for prevention and translational research.

ENERGY BALANCE AND THE DEVELOPMENT OF CHILDHOOD OBESITY

Childhood obesity fundamentally results from sustained energy (caloric) imbalance, that is, greater energy intake than expenditure needed for normal child growth. Under conditions of energy balance, there is sufficient energy intake to support healthy growth and development. Under conditions of positive energy balance, total energy intake exceeds the total energy expenditure necessary for healthy growth and can promote obesity (Faith, Stettler, & Stallings, 2005). Goran has shown that obesity in young children can result from a daily energy imbalance as subtle as 2% of daily energy requirements, or approximately 30 cal/day, if sustained over time (Goran, 2001). Thus, the daily energy imbalance necessary to become obese is not very large and, at least in early childhood, can develop from consuming only a few extra cookies or half a can of soda each day (beyond a child's basic caloric needs).

In principle, obesity-promoting genes can promote excess energy intake, decreased energy expenditure, or disrupt both pathways. The focus of this chapter is on how obesity-promoting genes influence specific eating patterns and food preferences that, ultimately, promote positive energy balance. Because the daily caloric imbalance necessary to become obese in early childhood may be subtle (~30 cal/day), the eating patterns that promote positive energy balance may also be subtle and therefore challenging to measure. Thus, as reviewed below, precise laboratory measures and validated questionnaires have been used to test whether certain eating patterns contribute to excess weight gain in obese-prone children.

FAMILIAL TRANSMISSION OF OBESITY

Parental obesity status is arguably the strongest and most reliable predictor of a child's obesity risk status and is likely due to both shared environmental and genetic influences (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). Simply put, obese parents tend to have obese children and

thin parents tend to have nonobese children. Moreover, as demonstrated as far back as 1936 (Gurney, 1936), the relationship between parental obesity status and child obesity follows a "dose response" such that children with one obese parent are more likely to become obese than are children with no obese parents. Moreover, children with two obese parents are more likely to become obese than are children with no or one obese parents.

Whitaker and colleagues examined obesity prevalence in young adulthood as a function of the presence or the absence of obesity at various time points throughout childhood as well as the presence or the absence of obesity in the child's parents (Whitaker et al., 1997). After 6 years of age, the probability of a child becoming an obese adult exceeded 50% for obese children compared with approximately 10% for nonobese children. In addition, the risk of adult obesity was significantly greater if either the child's mother or father was obese. That is, parental obesity more than doubled the risk of obesity in adulthood among both obese and nonobese children, especially those under 10 years of age. The authors found that among nonobese 1- and 2-year olds, those with at least one obese parent had a greater chance of being obese as adults compared to those without an obese parent (28% versus 10%). These findings illustrate the importance of family risk and, more specifically, parental obesity status in determining a child's risk for becoming an obese adult.

"HERITABILITY" OF OBESITY

That obesity "runs in families" is well established, as indicated by studies in the prior section. Teasing apart the influence of genetic and home environmental influences, however, is much more complicated. There have been decades of studies using twin, adoption, and other family designs to test the so-called heritability of body weight and obesity in childhood (Wardle, 2005). Heritability (h^2) refers to the percentage of variability in a trait that is due to genetic differences. Thus, heritability estimates of 20, 50, and 80% reflect relatively smaller, moderate, and larger genetic contributions to a trait, respectively. A trait that is entirely due to genetic factors has a heritability of 100%. Heritability estimates do not identify *specific* genes per se but rather provide a sense of the overall magnitude of genetic influences on the trait in question.

Results from twin studies suggest that genetic factors explain 50–90% of the variance in body mass index (BMI, kg/m^2) (Maes, Neale, & Eaves, 1997). Over half of the variability in children's body size, using measures such as BMI or total body fat stores, is due to genetic factors. For example, Faith et al. (1999) found the heritability of BMI and body fat percentage to be 86 and 76%, respectively, in a sample of 66 pairs of 3- to 17-year-old twins residing in the New York metropolitan area (Faith et al., 1999). Koeppen-Schomerus et al. found the heritability of weight (corrected for height) in a population-based sample of 608 MZ and 1210 DZ twin pairs from the United Kingdom to be 64% for boys and 61% for girls (Koeppen-Schomerus, Spinath, & Plomin, 2003). Collectively, the evidence for a strong genetic component to child weight status is well

established (Grilo & Pogue-Geile, 1991; Koeppen-Schomerus, Wardle, & Plomin, 2001; Stunkard et al., 1986; Wardle, 2005).

CAN OBESITY-PROMOTING EATING BEHAVIORS AND PREFERENCES BE INHERITED?

Obesity-promoting genes may "play out," in part, through eating traits that may also be transmitted within families. Indeed, a series of studies have tested whether there is an association among parents and children for food preferences and dietary intake patterns. These studies have established a small-to-moderate familial resemblance to eating phenotypes (Birch, 1980; Faith et al., 2004b; Laskarzewski et al., 1980; Logue, Logue, Uzzo, McCarty, & Smith., 1988; Pliner, 1983; Pliner & Pelchat, 1986; Rozin, Fallon, & Mandell, 1984; Skinner, Carruth, Wendy, & Ziegler, 2002). Thus, parents who eat plenty of fruits and vegetables and fewer chips tend to have children who, also, eat fruits and vegetables and less chips compared to other children. While useful in showing that eating patterns run in families, these studies could not disentangle the extent to which the familial resemblance is due to genetic and nongenetic home environmental factors (Faith, 2005).

There is now growing evidence that certain child eating patterns and food preferences are, in fact, heritable. A UK study (Breen, Plomin, & Wardle, 2006) comprising 428 twin pairs, 4–5 years old, found evidence for modest genetic influences on children's dessert preferences ($h^2 = 20\%$) but larger genetic influences on vegetable ($h^2 = 37\%$) and fruits ($h^2 = 51\%$) preferences. Child preferences for protein ("meat and fish") were even higher ($h^2 = 78\%$). Other studies have shown moderate heritability of sweet taste preferences in UK adult twins (Keskitalo et al., 2007b) and in Finnish families (Keskitalo et al., 2007a). There is also evidence that food "neophobia," which is reluctance to eat unfamiliar foods, is heritable in adults (Knaapila et al., 2007) and children (Cooke, Haworth, & Wardle, 2007). Finally, Faith et al. recently found that there is a significant genetic influence on a number of daily food intake patterns in 7-year-old boys and girls (Faith, Rhea, Corley, & Hewitt, 2008). This study examined the magnitude of genetic and environmental influences on 24-h food and beverage intake in 7-year-old children. Among boys, heritability estimates ranged from 12% (fish and lemon intake) to 79% (peanut butter and jelly intake). Among girls, heritability estimates ranged from 20% (bread and butter) to 56% (fish and lemon). In general, there was stronger evidence for genetic influences on 24-h food intake levels among boys than girls.

HIGH-RISK RESEARCH DESIGNS TO STUDY EATING TRAITS CONTRIBUTING TO CHILDHOOD OBESITY

Overview of High-Risk Design

That parental obesity confers a strong risk of obesity in offspring provides the opportunity to study behaviors contributing to positive energy

balance in obese-prone children. This research design, a so-called high-risk design, is especially informative when high-risk children are followed prospectively and when they can be compared to "low-risk" children (i.e., children born to two thin parents). As Wardle and colleagues noted, "Parental obesity can therefore be used as a marker of a higher genetic risk of obesity for young children who are not yet overweight, providing the opportunity to characterize the obesity risk phenotype before the situation is complicated by the multitude of biological, psychological and social consequences of obesity" (p. 971; Wardle, Guthrie, Sanderson, Birch, & Plomin, 2001a).

The high-risk design can also be informative for testing gene–environment interactions. To the extent that high-risk children gain more fat than do low-risk children in response to certain environments (e.g., eating at fast-food restaurants), this would reflect a gene–environment interaction. Children who are born with a slight or strong genetic predisposition will be more likely to become obese as exposure to obesogenic environmental cues increases. By contrast, children who are genetically resistant to obesity will be less responsive to environmental cues for obesity. These children may show minimal weight gain in response to environments that, for many or most other children in the population, would cause excess weight gain (Loos & Bouchard, 2003). The high-risk design can be useful for testing these questions of gene–environment interaction.

The Infant Growth Study

The University of Pennsylvania's Infant Growth Study (IGS) illustrates the use of the high-risk design to identify behavioral determinants of obesity onset in obese-prone versus obese-resistant children (Faith et al., 2004a, 2006; Kral et al., 2008; Stunkard, Berkowitz, Stallings, & Schoeller, 1999b, 1999a; Stunkard, Berkowitz, Schoeller, Maislin, & Stallings, 2004). The study was initiated approximately 15 years ago and, as of the writing of this chapter, still continues. The IGS cohort consists of 82 families that, at enrollment, included 41 infants born at high risk and 41 infants born at low risk for obesity. Risk status was based on mothers' pre-pregnancy BMI, with low-risk and high-risk families defined as mothers having a BMI <33rd percentile for US women their age and >66th percentile, respectively. By comparing traits on which the groups differ, from birth through (currently) age 15 years, investigators have gained insights into the pathways by which obesity may develop in children with a strong familial predisposition.

A preliminary issue examined by the IGS investigators was to identify the age when the high-risk and low-risk groups started to show differences in body fat during growth. Initial reports characterized different patterns of fat and lean body mass accretion through the first 6 years of life. Specifically, the size and body composition of high-risk and low-risk children did not differ by 2 years of age, although by age 4, the weight, the BMI, and the lean body mass of the high-risk children were significantly greater than those of the low-risk children. The groups did not yet differ in fat mass. By 6 years of age, however, the fat mass of the high-risk group had become much greater than that of the low-risk group

and differences in weight, BMI, and lean body mass continued to increase (Berkowitz, Stallings, Maislin, & Stunkard, 2005). A graphic in the original report shows the growth curves for body fat measures of individual high-risk and low-risk children during the first 6 years of life. As displayed in the graphic, the low-risk group of children showed relatively homogenous and low levels of body fat that did not increase significantly over time. High-risk children, by contrast, showed greater accretions in body fat that primarily occurred between 4 and 6 years of age. At age 6, approximately one-third of the high-risk children were overweight or obese (defined as a BMI $\geq$85th percentile) compared to roughly 3% of the low-risk children. These findings suggest that the ages of 4–6 years may be a critical window for the accretion of excess body fat in high-risk children.

A separate series of analyses attempted to identify behavioral predictors of excess weight or fat gain in this sample. One of the first findings pointed to the trait of "nutritive sucking rate" – that is, the rapidity or intensity with which an infant sucks on a bottle. This behavioral trait can be measured in the laboratory using procedures pioneered by Medoff-Cooper and colleagues (Medoff-Cooper, 1991; Medoff-Cooper & Ray, 1995), in which infants are given the opportunity to suck on a bottle with a rubber nipple that has an attached transducer; this transducer measures changes in volume pressure as the infant sucks on formula. Stunkard et al. compared high-risk and low-risk children with respect to sucking rate at 3 months of age, along with three-day energy intake, total energy expenditure, sleeping energy expenditure, and other measures (Stunkard et al., 1999b). Results indicated that the only variable discriminating the two groups at 3 months of age was rate of sucking, with high-risk children demonstrating a greater sucking rate compared to low-risk children. Moreover, three-month sucking rate but none of the energy expenditure measures predicted infant weight status at 12 months. Interestingly, similar findings were also found in a separate prospective cohort study of infants in Stanford, California (Agras, Kraemer, Berkowitz, Korner, & Hammer, 1987). Hence, excess sucking rate may be a trait through which obesity-predisposing genes operate behaviorally in the first months of life.

At ages 4–6 years, other behavioral traits were examined in the IGS cohort and were found to differ among high-risk and low-risk youths. For example, intake of sugar-sweetened beverages (servings/day) was increased and milk intake was reduced among high-risk compared to low-risk children (Kral et al., 2008). Moreover, among low-risk children but not high-risk children, greater consumption of milk was associated with reduced intake of sugar-sweetened beverages. Among high-risk children, however, this effect was not present, suggesting that high-risk children were not showing behavioral displacement of the "healthier" beverage choice (milk) for the "less healthy" beverage choice (soda). Thus, the familial predisposition to obesity may operate through beverage choice selections. Indeed, other studies have shown that excess beverage consumption is associated with increased obesity risk, primarily in children who are already overweight or obese (Downs, Marshall, Ng, & Willows, 2008).

Another noteworthy finding from the IGS cohort concerned the trait of "disinhibited eating," which refers to the tendency to eat in response to food cues despite being full. Among adults, disinhibited eating is one of the strongest and most consistent predictors of excess body fat (Elfhag & Rossner, 2005). For young children, laboratory procedures can assess disinhibited eating using an "eating in the absence of hunger" paradigm (Birch, Fisher, & Davison, 2003; Cutting, Fisher, Grimm-Thomas, & Birch, 1999; Fisher & Birch, 2002; Fisher et al., 2007). This procedure has children consuming ad libitum (as much as desired) a lunch or a dinner meal in the laboratory until they are full. Approximately 10 min after the meal, children are taken to a separate room that has access to games, toys, and a variety of different snack foods which children are allowed to eat (e.g., chips, popcorn, chocolate candies). The amount of food that children eat from the snack food represents "eating in the absence of hunger" or disinhibited eating. In the IGS cohort, high-risk boys ate twice as many calories in the absence of hunger compared to low-risk boys, although there was no difference in girls (Faith et al., 2006). Thus, genes for obesity may partially operate through a greater tendency to eat in response to external food cues, at least among boys. Interestingly, a recent large-scale genetics study investigating the onset of obesity in Hispanic youth established that eating in the absence of hunger is a highly heritable behavioral trait in youth, with a heritability estimate of ~50% (Fisher et al., 2007), and is associated with elevated BMI.

In sum, the traits of increased sucking rate (Stunkard et al., 1999b), excess intake of sugar-sweetened beverages (Kral et al., 2008), increased eating in the absence of hunger (Faith et al., 2006), and increased total caloric intake in the free living environment (Faith et al., 2008) have been found to differentiate high-risk and low-risk children in the IGS cohort and/or to predict excess weight gain. These suggest potential behavioral pathways leading from family risk to obesity phenotype, and we are continuing to explore during the teenage years.

Twins Early Development Study (TEDS)

From the larger UK-based "Twins Early Development Study (TEDS) (Trouton, Spinath, & Plomin, 2002), 200 children were selected from families with overweight/obese parents and 228 children were selected from families with normal-weight/lean parents (Wardle et al., 2001a). These children were investigated with respect to a variety of eating measures and traits to examine how familial risk to obesity may play out through eating patterns. Compared to children of normal-weight/lean parents, children of overweight/obese parents had significantly lower preference ratings for vegetables, were more responsive to food cues, and had higher desire for drinks (all based on the maternal report). The two groups of children did not differ significantly with respect to food intake as measured by a food frequency questionnaire and by observed intake of palatable foods.

In sum, high-risk designs can be a useful strategy when ascertainment of related individuals, including twins, is not feasible. Identifying behavioral traits that discriminate children born at high risk versus low

risk for becoming overweight can help identify behavioral mechanisms by which genetic vulnerability expresses itself. These designs can be informative for cross-sectional comparison but are most informative in the context of prospective analyses that test whether behaviors mediate the relationship between risk status and subsequent adiposity gain.

SPECIFIC GENETIC ASSOCIATIONS WITH OBESITY RISK AND EATING BEHAVIOR

Genome-wide association studies and other genetic association studies have identified specific common gene variants associated with increased risk of obesity, and with intermediate eating phenotypes, in children and adults. The first common gene variant to be identified and associated with obesity risk was a variant in the *FTO* gene (Frayling et al., 2007). Roughly one in six people are homozygous for the *FTO* risk allele (i.e., have inherited two copies of the "risky version" of the gene, one each from both of their parents), and these individuals have a 1.7-fold increased odds of obesity compared to those with no risk allele. The association has been shown to be robust in multiple populations (Cha et al., 2008; Chang et al., 2008; Dina et al., 2007; Hinney et al., 2007; Hunt et al., 2008; Scuteri et al., 2007).

Expression of the *FTO* gene is greatest in the hypothalamus (Gerken et al., 2007) and varies with acute food deprivation (Stratigopoulos et al., 2008). Moreover, studies in humans have found a significant association between the *FTO* variant and self-reported and observed energy intake (Speakman, Rance, & Johnstone, 2008; Wardle et al., 2008) but have found no association with energy expenditure, i.e., metabolism or physical activity (Speakman et al., 2008; Wardle et al., 2008). These findings suggest that the *FTO* gene may be more likely to exert its effects on obesity risk through a behavioral, eating causal pathway than an explicit physiological, metabolic causal pathway. This further supports the emerging picture that at least some of the inherited susceptibilities to obesity displayed in children and adults arise as a result of a genetic susceptibility to specific eating behaviors. Additional common gene variants are being identified which also appear to be associated with obesity risk, such as the *MC4R* gene (Loos et al., 2008).

EMOTIONAL EATING AND OBESITY

One behavioral trait which has been explored extensively in obesity research generally, but to date has received relatively little attention in genetic association studies, is emotional eating. Emotional eating has been described as "the tendency to eat in response to affective state" (Waller & Osman, 1998). The trait has emerged as a reasonably stable construct and can be measured in adults using the emotional eating subscale of the Dutch Eating Behaviour Questionnaire (DEBQ) (van Strien, Frijters, Roosen, Knuiman-Hijl, & Defares, 1985) and the Emotional Eating Scale

(EES) (Arnow, Kenardy, & Agras, 1995). It has also been found that the Hunger and Disinhibition scales of the Three Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985) cluster to create an emotional eating factor (Karlsson, Persson, Sjostrom, & Sullivan, 2000). Masheb and Grilo (2006) published the Emotional Overeating Questionnaire (EOQ) (Masheb & Grilo, 2006). For children, the Children's DEBQ (DEBQ-C) (van Strien & Oosterveld, 2008), the Children's EES (EES-C) (Tanofsky-Kraff et al., 2007), and the emotional overeating scale of the Children's Eating Behavior Scale (CEBQ) (Wardle, Guthrie, Sanderson, & Rapoport, 2001b) are available to measure emotional eating tendencies in youth. There is evidence that emotional eating tendencies may be elevated among obese compared to nonobese youth (Tanofsky-Kraff et al., 2008). Although one study has demonstrated a heritability estimate of 60% for emotional eating (Tholin, Rasmussen, Tynelius, & Karlsson, 2005), we are not aware of any other studies which have examined genetic associations with emotional eating. Further research is needed to identify whether emotional eating tendencies in youth are heritable, and whether there are specific gene variants which increase the likelihood of this important behavioral trait being expressed.

TRANSLATING GENETIC INFORMATION ABOUT OBESITY RISK INTO TREATMENT AND PREVENTION: THE CASE OF GENETIC TESTING

There are several potential applications of genetic information in the treatment and prevention of complex conditions such as obesity (Collins, Green, Guttmacher, & Guyer, 2003). First, genetics research increases understanding of the etiology and causal pathways to obesity. Second, it may help develop new drug treatments and identify pharmacological targets. Third, it may help stratify patient groups so that individuals are given a drug treatment only if it is known to be effective and safe for their personal genotype (i.e., pharmacogenomics). Fourth, providing individuals with information about their genetic susceptibility to obesity may motivate them to make lifestyle changes to reduce the chance that they will become obese (Khoury, Davis, Gwinn, Lindegren, & Yoon, 2005).

It is possible that providing genetic information about obesity and related disease (e.g., type 2 diabetes) risk, based on genotype, may motivate some individuals to make healthier lifestyle changes (Gable, Sanderson, & Humphries, 2007). However, as Janssens and others have highlighted, there is currently little evidence to support the claim that people will use genetic information as a motivator to change behavior (Janssens, Gwinn, Valdez, Narayan, & Khoury, 2006). Research is just beginning to address whether genetic information about obesity risk will be acceptable to individuals and whether it will help or hinder behavior change interventions. Two studies suggest that genetic testing for obesity risk may be acceptable to adults both for themselves (Segal, Polansky, & Sankar, 2007b) and for their children (Segal, Polansky, & Sankar, 2007a).

To date, only three studies have directly examined the potential psychological and behavioral impact of personal genetic testing for obesity risk (Frosch, Mello, & Lerman, 2005; Harvey-Berino et al., 2001; Sanderson, Persky, & Michie, 2010). The first was a small study in which overweight women were provided with personal genetic test results for a *b3AR* gene variant believed at the time to be associated with increased obesity risk (Harvey-Berino et al., 2001). There were no differences among individuals who were informed that they did or did not have the adverse gene variant in terms of confidence in their ability to change behavior.

Frosch and colleagues randomly assigned nonobese students to review one of four hypothetical scenarios (or 'vignettes') and asked them to imagine how they would feel if they received one of the four hypothetical test results (Frosch et al., 2005). They found no differences between participants given a high-risk result based on a genetic test and those given the same result based on a hormone test in a number of outcomes, including perceived risk of obesity and intention to eat a healthy diet. However, participants receiving the genetic high-risk result reported lower perceived control over behavior than did participants receiving the genetic average-risk result.

Sanderson and colleagues investigated whether people respond differently to genetic risk information when the genetic variant is described as exerting its obesogenic effect through an eating-related causal pathway versus a more explicit physiological metabolism-related causal pathway (Sanderson et al., in press). Participants were randomly allocated to review one of five hypothetical scenarios in which they were asked to imagine they had received the following: a genetic test result indicating high eating-based or metabolism-based risk of obesity; an enzyme test result indicating high eating-based or metabolism-based risk of obesity; or no risk information. The groups receiving test results indicating increased obesity risk reported greater perceived risk and intention to eat healthily than did the no risk information group, regardless of whether or not the test was described as genetic or nongenetic (enzyme), or as acting through an eating-based or a metabolism-based causal pathway.

Although the results of these few studies present a somewhat mixed picture, overall they suggest that genetic testing for obesity risk might motivate behavioral change without causing adverse effects. Further behavioral research is needed to assess the clinical utility (i.e., the risks and benefits) of genetic testing for susceptibility to common, complex traits such as obesity (Sanderson, Wardle, & Humphries, 2008).

CONCLUSIONS

There is compelling evidence that childhood obesity "runs in families" and that genetic factors are responsible for much of this familial transmission. Obesity-predisposing genes appear to operate, in part, through eating behaviors that are "conduits" to positive energy balance and the development of obesity. A priority for future research is to identify these specific eating traits and the genes that influence them. With respect to

treatment and prevention, it is a reasonable hypothesis that child genotype will influence individual variations in response to clinic-based and public health interventions. This is a burgeoning area of research that is lacking in data. Knowing whether intervention response is moderated by child genotype will be important for advancing basic understanding of regulatory weight control mechanisms and, ultimately, determining whether specific treatments should be targeted to obese (or obese-prone) youth with specific genetic profiles. In the short run, the answer to the latter question remains unclear.

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15

Tobacco and Alcohol Use Behaviors

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BACKGROUND

Substance use disorders (abuse and dependence as defined by the DSM-IV) are common; considering all drug categories nicotine dependence and alcohol dependence are generally the most prevalent. These disorders often cluster within individuals and within families, are the source of familial problems and serious morbidity and mortality, and exact great costs from society. Although evidence-based treatments of substance use disorders exist, the often chronic relapsing–remitting nature of these problems underscores the importance of research that seeks to better understand the biological (as well as social) contributions to risk for these disorders. Genetic studies offer one such approach and this chapter reviews much of that body of work.

Epidemiology

Substance use is common in the USA beginning in adolescence. About two thirds and one third of 10th graders report that they have used alcohol and cigarettes, respectively, with 15% having tried smokeless tobacco products; with increasing age across adolescence that lifetime use increases (Johnston, O'Malley, Bachman, & Schulenberg, 2007). Often onset of substance use *and* progression to dependence occurs in adolescence; peak risk of onset of both alcohol and cannabis dependence occurs at age 18 in the USA (Li, Hewitt, & Grant, 2004; Stinson, Ruan, Pickering, & Grant, 2006). Among adults in the USA about 1 in 12 meet the criteria for an alcohol use disorder (abuse or dependence) and 1 in 8 are nicotine

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dependent in a given year (Grant, Hasin, Chou, Stinson, & Dawson, 2004; Stinson et al., 2005).

Within-Individual Clustering of Disorders

Substance use disorders often do not occur in isolation and numerous reports have provided evidence for a strong association between tobacco and alcohol use. The 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) showed that rates of tobacco use were lowest among individuals who were lifetime abstainers of alcohol, increased with levels of alcohol consumption, and were highest among alcohol-dependent subjects. Similarly, alcohol-dependent men and women showed a significant increase in risk for nicotine dependence (11.7 times increased risk for men and 16.3 times increased risk for women) (Falk, Yi, & Hiller-Sturmhofel, 2006). Furthermore, individuals with nicotine and alcohol problems also display elevated rates of mood, anxiety, and personality disorders, including antisocial personality (Grant et al., 2004; Stinson et al., 2005). The same patterns are seen for alcohol and drug dependence (Conway, Compton, Stinson, & Grant, 2006; Goldstein et al., 2007; Grant et al., 2005; Li et al., 2004). Thus, these disorders are not only common but also often complicated by the co-occurrence of multiple other disorders within the same individual.

Family Effects and Familial Clustering

Substance use disorders and other related risk behaviors (such as conduct disorder and antisocial personality disorder) are common and can be viewed both as an individual problem and as a family problem. Alcohol/drug dependence and/or intoxication is commonly associated with domestic violence, divorce, child abuse (and placement in foster care), and inadequate parental monitoring (see Leonard & Eiden, 2007 for review). Those substance-dependent family members are also at increased risk for serious morbidity and mortality (both through ill effects of the drug of abuse and through accidents during intoxication, among other reasons). Nicotine, alcohol, and illicit drugs have been ranked as 3 of the top 10 preventable causes of death in the USA (Mokdad, Marks, Stroup, & Gerberding, 2004). In addition, illicit drug use, driving while intoxicated, and antisocial behavior increase risk for incarceration. Thus parents with substance use disorders may struggle to provide a safe stable home environment with adequate supervision for their children.

These disorders cluster within families and substance use disorders emerge at high rates among offspring of substance-dependent parents (relative to non-substance-dependent parents) (Johnson & Leff, 1999), sometimes perpetuating multigenerational patterns; genetic risk offers one important explanation for those patterns. Alcohol exposure in utero is known to cause fetal alcohol spectrum disorders leading to a range of negative developmental problems among these children. Such individuals therefore need special educational and counseling programs to learn to handle these behavioral issues (Green, 2007). Similarly, there

is evidence that maternal smoking during pregnancy is associated with increased risk of negative behavioral outcomes for the offspring, including conduct disorder, attention-deficit hyperactivity disorder, oppositional defiant disorder, and smoking behavior (Shenassa et al., 2003). The impact of substance use on the developing adolescent brain is an area of high concern and active research. Substance use sometimes contributes to adolescent school failure, incarceration, suicide, and accidental injury or death. Many conduct-disordered substance-dependent adolescents demonstrate poor affect regulation, limited frustration tolerance, impulsivity, risk-taking propensity, discount delayed rewards and pursue short-term rewards despite long-term consequences (Bechara, 2001, 2005; Crowley, Raymond, Mikulich-Gilbertson, Thompson, & Lejuez, 2006; Dahl, 2001; Field, Christiansen, Cole, & Goudie, 2007; Thompson, Whitmore, Raymond, & Crowley, 2006). In many instances, parents, still dealing with substance abuse and other comorbid conditions of their own, are faced with parenting children and adolescents with a difficult temperament and active substance use problems.

Morbidity, Mortality, and Costs to Society

Worldwide alcohol-related morbidity and mortality are well recognized (Grimm, 2008), contributing to about 3.2% of all deaths globally and about 58 million disability-adjusted life years (WHO, 2008). Costs to society from alcohol-related harms are great. In 1992 in the USA alone, the estimated cost of alcohol abuse and dependence was $148 billion and much of that economic burden is borne by those who do not abuse alcohol (Harwood, Fountain, & Fountain, 1999). Cost estimates of other countries, such as Germany (Konnopka & Konig, 2007) and Canada (Rehm et al., 2007), are equally concerning.

Summary

In summary, alcohol, tobacco, and other substance use and dependence pose serious problems for children and their families. In addition to comorbidity observed between alcohol, tobacco, and other substance use disorders, these disorders also occur frequently in combination with additional problems, such as mood, anxiety, and personality disorders, and problems at school and in the workplace. In this chapter we focus on research aimed at understanding the underlying genetic vulnerabilities which contribute to these disorders; this knowledge may facilitate the development of improved prevention and treatment approaches.

Unfortunately, genetic studies of complex disorders offer many challenges. While many Mendelian disorders have been mapped to genetic determinants, complex traits are generally thought to be affected by many genes of relatively small effect. To date relatively few clear genetic contributors to risk for substance use disorders have been identified. Still molecular advances in the field are progressing at a rapid pace as are analytic methodology, and this offers promise for future discoveries. This chapter (1) reviews the approaches employed thus far to search for genetic

determinants of risk for substance use disorders, (2) highlights the most supported genetic findings associated with substance use disorders, (3) presents the extensive, but less empirically supported, research database of genetic association studies of substance use disorders, and (4) lastly reviews some of the possible implications of future genetic discoveries for the individual, families, and society.

APPROACHES TO GENE DISCOVERY

Heritability

Prior to embarking on expensive and labor-intensive studies to discover genetic contributors to risk for a disorder, it is imperative to first demonstrate the heritability of the relevant phenotypes. There are several lines of evidence demonstrating that genetic factors are important for predicting long-term tobacco use (Heath, Madden, & Martin, 1998; Swan, Carmelli, & Cardon, 1997b). Several studies have demonstrated that significant genetic effects contribute to smoking, typically accounting for approximately 50% (28–84%) of the total variance (Swan & Carmelli, 1997a). Similarly, a variety of twin, adoption, and family studies have shown that genetic components play a role in the development of alcohol dependence (Cadoret, Cain, & Grove, 1980; Cloninger, Bohman, & Sigvardsson, 1981; Cotton, 1979; Heath et al., 1997; Hrubec & Omenn, 1981; Kaprio et al., 1987; Sigvardsson, Bohman, & Cloninger, 1996; True et al., 1999).

The high level of comorbidity between alcohol and tobacco dependence raises questions about whether co-occurrence is caused by a common genetic etiology or is driven by strong, common environmental contributors. Recent studies support the theory that common genetic factors may contribute to the concurrent use of these two substances. Evaluating tobacco, alcohol, and coffee use in adult male twins, Swan, Carmelli, and Cardon (1996) found that a common pathway model provided a good fit to the data. This finding was extended to the study of heavy use of tobacco and alcohol, where a single latent factor could explain the joint heavy use of these two substances (Swan et al., 1997b). Madden, Heath, and Martin (1997) conducted a multivariate analysis that supported the presence of a common genetic influence between subjective response to alcohol and smoking, although this effect was only seen in women. In men, True et al. (1999) found a genetic correlation of 0.68 for co-occurrence of nicotine and alcohol dependence. Looking at overlapping use of tobacco, alcohol, and caffeine in a large population-based twin sample, Hettema, Corey, and Kendler (1999) found evidence that the common use of these three substances is mediated by both nonspecific shared substance use factors and substance-specific factors. In a community-based sample of older female twins, a significant genetic correlation between problem drinking and ever smoking was detected (Hopfer, Stallings, & Hewitt, 2001). More recently, Young, Rhee, Stallings, Corley, and Hewitt (2006) reported significant common genetic influences for tobacco, alcohol, and marijuana

problem use, with shared environmental influences contributing to more substance-specific problem use. These traditional univariate and multivariate biometrical modeling approaches have provided a solid foundation in terms of demonstrating the importance of individual genetic factors contributing to behaviors related to individual substances, as well as providing evidence that some genetic factors are likely to be common across disorders.

Approaches in the Search for Genetic Contributors

For any complex disorder, including psychiatric disorders such as substance abuse, conduct disorder, or depression and traditional physiological disorders such as cardiovascular disease, diabetes, or obesity, researchers are challenged by the fact that common diseases typically are caused by a complex combination of multifactorial risks that include genetic, environmental, and behavioral factors. For example, geneticists are not searching for "the" gene contributing to a specific disorder, because multiple genes in any single individual are likely to contribute to an individual's overall risk of disorder. Likewise, different genes or different variants in the same genes may be important in different subsets of the population, dependent on many factors including genetic heterogeneity among ethnic groups, cultural differences, and other environmental conditions. Thus, the clinical outcome of a patient depends on many factors in addition to the DNA sequence variation within a single gene, thereby making the effect of any specific mutation or variation very challenging to identify (Zondervan & Cardon, 2004).

With the advent of molecular genetics technologies over the last 30 years, substance abuse researchers have been able to interrogate specific mapped variations in the human genome. As the advances in molecular genetics technology continue to explode (with "affordable" technologies for complete re-sequencing of the entire human genome on the horizon), similar advances in methods of statistical genetics have been developed to carefully analyze and interpret the molecular data in the context of behavior. There are three main approaches researchers have employed to identify genes or genomic regions believed to be associated with complex genetic disorders: linkage studies, candidate gene studies, and genome-wide association studies.

Linkage Approach

Linkage analysis is a classic method for localizing genes that is based on the co-segregation of genetic markers and traits in families over several generations (Laird & Lange, 2006). Genetic linkage analysis is based on the fact that few recombination events occur in any single generation, so broad chromosomal regions are shared between parents and children and between siblings. Therefore, if a particular marker variant is observed in affected children more often than unaffected offspring, it is inferred that a gene with a functional effect is located nearby the marker. Using

linkage approaches, large chromosomal regions, called quantitative trait loci (QTLs), are identified as genomic areas likely to contain genes which contribute to a particular disease. QTL methods have proven very successful for identifying genes involved in recessive, highly penetrant diseases. However, using linkage to find genes for complex disorders has been more challenging, because the QTLs identified have yielded lower levels of statistical significance and have been difficult to replicate across studies (Dean, 2003). Furthermore, most linkage regions span millions of DNA base pairs which include numerous candidate genes, making it difficult to prioritize which genes should be further evaluated. Fortunately, new molecular technologies have improved our ability to examine a dense array of single nucleotide polymorphisms (SNPs) across previously identified QTLs, which is likely to yield more success in this area.

Candidate Gene Approach

Candidate gene association analysis has been used historically for "case–control" designs whereby unrelated individuals are recruited into two groups that differ in the phenotype of interest and a biologically plausible candidate gene is examined. It is based on the idea that subjects who fall into the "affected" status are more likely to carry a particular allelic variant of a genetic marker than those who are "unaffected." Data are most simply analyzed using a standard chi-square analysis to compare genotypic frequencies between cases and controls or using Student's *t* tests to compare mean scores of a quantitative trait by genotype.

Whole Genome Association Approach

Recent advances in technology which allow rapid simultaneous genotyping of hundreds of thousands SNPs in many individuals have led to the feasibility of whole genome associations (WGA) studies. In these studies, millions of SNPs are examined in a case–control or family design to identify localized gene regions for a particular phenotype (Risch, 2000). These advances might be seen by some to suggest that using linkage to localize large genomic regions is a thing of the past, but advanced statistical approaches to analyze WGA data have been developed to utilize family-based approaches with substantial power (Laird et al., 2006). The unprecedented scale of these studies and the exciting possibilities for rapid advancement of knowledge have been demonstrated in several recent publications and replications of WGA studies, as recently reviewed (Neale & Purcell, 2008). This is particularly encouraging, since all family data, previously collected when linkage was the gene-mapping tool of choice, can now be examined using the new technologies and analytical approaches.

SUMMARY OF MAJOR FINDINGS

Linkage Studies of Alcohol and Tobacco Phenotypes

Numerous linkage studies have attempted to identify regions of the genome that contribute to nicotine dependence and alcohol dependence and/or abuse. These studies have examined tobacco dependence and alcoholism as well as behaviors and physiological measures associated with problem use.

Many of the reported linkage studies have been the culmination of data analyses using samples collected as part of large ongoing studies in the USA. These are the Collaborative study on the Genetics of Alcoholism (COGA) and the Framingham Heart Study. Several other populations have been used including samples of American Indians (Ehlers & Wilhelmsen, 2005; Goldman et al., 1993), Finnish alcoholic criminals (Lappalainen et al., 1998), cocaine and opiate users (Gelernter et al., 2007), individuals with schizophrenia (Faraone et al., 2004), individuals selected for panic disorder (Gelernter et al., 2004), antisocial substance users ascertained through an adolescent treatment-based clinical facility (Stallings et al., 2003), and more recently a group of mid-south tobacco families (MSTF) (Li et al., 2008).

There have been a few QTLs that have been replicated across different studies. For alcohol, chromosomes 1, 4, 6, 7, 11, 12, 15, and 16 have been linked to alcohol phenotypes in multiple studies and should be targeted in future research. Likewise, chromosomes 1, 2, 4, 5, 6, 7, 9, 10, 11, and 17 have been linked to tobacco phenotypes in multiple samples. In looking at QTLs common to alcohol and tobacco, peaks on chromosomes 1, 4, 6, and 11 have been identified by multiple studies in different populations with both tobacco dependence and alcoholism-related phenotypes, making them prime regions to search for genes contributing to the comorbidity of alcoholism and tobacco dependence. Some known genes on these chromosomes which are likely candidates are potassium channel-related proteins and tyrosine kinase on chromosome 1, the alcohol dehydrogenase (*ADH*) gene cluster on chromosome 4q, the μ-opioid receptor gene on chromosome 6, and chromosome 11p contains the dopamine receptor DRD4 in addition to several other genes involved in neurogenesis. In summary, linkage approaches have yielded several QTLs of interest that are being actively pursued using new dense SNP mapping technologies to narrow these genomic regions. The best known QTL "success" story is the association of the *GABRA2* gene and alcoholism (see section "γ-Aminobutyric Acid Receptor Genes" for details).

Association (Candidate Gene and Whole Genome Association) Studies of Alcohol and Tobacco Phenotypes

Association studies with tobacco dependence and alcoholism have primarily focused on candidate genes, though some studies have carried out whole genome associations (Bierut et al., 2007; Johnson et al., 2006; Uhl

et al., 2007). As with linkage studies, an assortment of different population samples have been studied and the research designs have included case–control, family studies, and population-based samples. Candidate genes generally fall into two classes: those whose protein products are known to participate in the metabolism of alcohol or nicotine and those that are involved in known reward/reinforcement neurological pathways, such as the dopamine reward pathway, the serotonin pathway, the opiate receptor genes, the *GABA* receptor genes, and the nicotinic acetylcholine receptor genes. Here we focus on the three classes of genes which have yielded the strongest and most consistent evidence for association with alcohol and tobacco behaviors: the alcohol and acetaldehyde dehydrogenase genes, *GABA* receptor genes with alcohol use behaviors, and the nicotinic acetylcholine receptor genes with nicotine addiction.

Alcohol and Acetaldehyde Dehydrogenase Genes

In humans alcohol is metabolized into acetaldehyde primarily by alcohol dehydrogenases in the liver and from acetaldehyde to acetic acid by acetaldehyde dehydrogenases in liver mitochondrion. Extrahepatic metabolism is completed by cytochrome P450 2E1 in microsomes and by catalase in peroxisomes (Zakhari, 2006). There are seven genes encoding alcohol dehydrogenases (*ADH1A*, *ADH1B*, *ADH1C*, *ADH4*, *ADH5*, *ADH6*, and *ADH7*) located head to tail on chromosome 4q22 and two main genes encoding acetaldehyde dehydrogenases (*ALDH2* and *ALDH1A1*) located on chromosomes 9 and 12, respectively (Edenberg, 2007; Edenberg et al., 2006). A third acetaldehyde dehydrogenase gene (*ALDH1B*) is also present on chromosome 9, but very little is known about this gene. Among these 10 genes, a number of known polymorphisms have been shown to lead to reduced activity of the enzyme product.

In addition, variations in many of these genes have been linked to alcoholism. Multiple studies have shown an association between alcoholism and polymorphisms in *ADH1B* and *ADH1C* (see Edenberg, 2007; Edenberg et al., 2006; Eng, Luczak, & Wall, 2007). However, it remains unclear whether the associations with *ADH1C* are direct associations with this gene or indirectly due to its proximity to *ADH1B* (Osier et al., 1999). A recent study by Ehlers and colleagues (2007) found evidence for a role of these genes in alcoholism among southwest California Indians as well. Of the other *ADH* genes, only *ADH4* has been convincingly associated with risk for alcoholism in multiple studies (Edenberg, 2007). However, there has been at least one report of an association between polymorphisms in *ADH7* and gastric metabolism of alcohol and between *ADH5* and *ADH6* and alcohol dependence (Luo et al., 2006).

Likewise, polymorphisms in *ALDH2*, particularly the *ALDH2*2* allele, have been consistently shown to be protective against alcoholism among Asian populations, but is essentially not present in individuals of European or African descent (Eng et al., 2007; Li, 2000; Luczak, Glatt, & Wall, 2006; Yoshida, 1994). Individuals heterozygous for the *ALDH2*2* allele have almost no detectable *ALDH2* activity in liver which leads

to an alcohol-induced flushing reaction and other highly adverse reactions (Crabb, Edenberg, Bosron, & Li, 1989). These adverse reactions are believed to confer a protective effect of *ALDH2*2* against alcoholism.

γ-Aminobutyric Acid Receptor Genes

The neurotransmitter γ-aminobutyric acid (GABA) acts as an inhibitor when it binds to neurons containing GABA receptors, of which there are three main types ($GABA_A$, $GABA_B$, and $GABA_C$), all of which are comprised of multiple subunits (Bettler, Kaupmann, Mosbacher, & Gassmann, 2004; Chebib, 2004; Mehta & Ticku, 1999; Olsen, Hanchar, Meera, & Wallner, 2007; Whiting, 2003). A wealth of research has shown that the GABAergic system plays a critical role in neuronal response to alcohol and nicotine (Boehm et al., 2004; Grucza & Bierut, 2006; Krystal et al., 2006). In addition to the GABA receptors themselves, there are a number of proteins that have been shown to associate with GABA receptors and proteins involved in GABA synthesis. Since all of these proteins are involved in modulating GABAergic pathways, they are all considered good candidate genes for association with nicotine and/or alcohol behaviors.

The $GABA_A$ receptors contain a chloride channel and genes for these subunits are primarily arranged in clusters on chromosomes 4, 5, 15, and on the X chromosome (Darlison, Pahal, & Thode, 2005). Chromosome 4 has been the focus of several studies, following the detection of a QTL peak in the COGA study (Edenberg, 2002; Foroud et al., 2000; Reich et al., 1998). An extensive survey of the four *GABA* genes (*GABRG1*, *GABRA2*, *GABRA4*, and *GABRB1*) by Edenberg et al. provided strong evidence for an association between *GABRA2* and alcoholism, but not the other three genes (Edenberg et al., 2004). This finding has been replicated in a separate European American sample (Covault, Gelernter, Hesselbrock, Nellissery, & Kranzler, 2004), a Russian sample (Lappalainen et al., 2005), and a German sample (Fehr et al., 2006). A separate study has provided support for the idea that certain *GABRA2* alleles may contribute to subjective response to alcohol (Pierucci-Lagha et al., 2005). This is an appealing model, since it fits well with the long-term studies showing that subjective response to alcohol is an excellent predictor of later alcohol use patterns (Schuckit, 1999; Schuckit & Smith, 1996, 2000; Schuckit, Smith, & Tipp, 1997; Schuckit et al., 2000). More recently, a follow-up to the initial COGA report has found an association between *GABRA2* and marijuana dependence and illicit drug dependence, where all of the association observed with alcohol dependence could be attributed to only those individuals with comorbid drug dependence (Agrawal et al., 2006). However, this is in contrast to the study by Covault et al. (2004), where the strength of the association increased when illicit drug-dependent subjects were excluded from the analysis. In a new report, Covault and colleagues investigated the extent of linkage disequilibrium between *GABRA2* and the adjacent *GABRG1* gene by genotyping additional SNPs in the intergenic region (Covault, Gelernter, Jensen, Anton, & Kranzler, 2007). They found evidence for association with SNPs near the *GABRG1* gene and alcohol dependence, which is in contrast to the initial report by Edenberg

et al. (2004). These conflicting results reiterate some of the challenges with which researchers struggle in conducting studies of drug dependence – allelic heterogeneity in different samples and definition of phenotype in the context of comorbid disorders. However, the accumulated evidence supports the hypothesis that the *GABRA2* gene contributes to alcohol behavior; whether it is specific or more general to other substances remains to be elucidated.

Nicotinic Receptor Genes

Nicotinic acetylcholine receptors are pentameric receptors in the superfamily of ligand-gated ion channels. Present throughout the brain, they are involved in the modulation of dopamine release in the mesolimbic system. Stimulated by both acetylcholine and nicotine, neuronal nicotinic acetylcholine receptors (nAChRs) are prime candidates for contributing to nicotine dependence. Furthermore, alcohol has also been shown to modulate the properties of these receptors. Nine α (α2 through α10) and three β (β2–β4) subunits have been identified. Of these α5 and β3 do not contain a binding site, but are believed to contribute to the pharmacological properties of receptors where they are found. Receptors are composed of α and β subunits, usually two α and three β or three β and two α, though some α subunit subtypes, α7, α8, and α9, form homomeric receptors. The receptor subunits occur in many combinations throughout the brain yielding diverse functional and pharmacological properties. They are grouped here for convenience, but many other combinations are possible (Dani & Bertrand, 2007; Gotti, Zoli, & Clementi, 2006).

Receptors composed of α4 and β2 subunits are the most prevalent type in the brain. Many studies have examined polymorphisms in the *CHRNA4* and *CHRNB2* genes which encode the α4 and β2 subunits with assorted results. A subset of polymorphisms in *CHRNA4* have been consistently associated with nocturnal frontal lobe epilepsy, establishing that genetic variation in this receptor subunit can dramatically affect receptor function and result in phenotypic change. However, conclusive evidence as to whether common polymorphisms in α4 and β2 present in populations affect smoking or alcohol behavior is still elusive. *CHRNA4* has been found to be associated with nicotine dependence measured by the Fagerstrom test for nicotine dependence (FTND) in at least three studies (Feng et al., 2004; Hutchison et al., 2007; Li et al., 2005) and alcoholism in Koreans (Kim et al., 2004). But equally many studies have failed to find an association with FTND or alcoholism (Bierut et al., 2007; Ehringer et al., 2007; Greenbaum et al., 2006; Silverman et al., 2000). Similarly, the vast majority of studies have found no evidence for association between nicotine dependence or alcoholism and *CHRNB2* (Bierut et al., 2007; Greenbaum et al., 2006; Li et al., 2005; Lueders et al., 2002; Silverman et al., 2000). Yet recently *CHRNB2* was shown to be associated with the endophenotype of early subjective effects to smoking and alcohol in a sample of Caucasian young adults (Ehringer et al., 2007), as well as smoking initiation in Israeli female students (Greenbaum et al., 2006), and heavy smoking in schizophrenia (Voineskos et al., 2007).

Nicotinic receptors containing β3 subunits are primarily found localized with α3 and β4 in the interpeduncular nucleus and medial habenula, whereas receptors with β3, α6, and β2 are found in the substantia nigra, VTA, striatum, and locus coeruleus (Gotti et al., 2006), often co-occurring with α4 and β2 subunits. The genes for α6 and β3 (*CHRNA6* and *CHRNB3*) are adjacent on chromosome 8, though there are many tissues in which one or the other is expressed, so they are unlikely to be co-regulated (Gotti et al., 2006). Recent genome-wide association studies and candidate gene studies have found strong associations with SNPs upstream of *CHRNB3* and nicotine dependence (Bierut et al., 2007; Hoft et al., 2008; Saccone et al., in press) and early subjective effects to tobacco (Zeiger et al., 2007). The β3 subunit does not contribute to the binding sites of the receptor, but is thought to stabilize the receptor as it is assembled and transferred to the cell surface. This characteristic led it to be somewhat ignored in the literature. Interestingly, as people are beginning to investigate the *CHRNB3* gene, this previously believed "minor" player appears to contain persistent genetic variations and these are likely to contribute to phenotype variation at the population level.

The genes coding the α3, α5, and β4 subunits occur contiguously on chromosome 15 and are thought to be co-regulated to some degree based on work examining the homologous cluster in the rat genome (McDonough & Deneris, 1997; Xu, Scott, & Deneris, 2006). The three subunits are co-expressed in the adrenal medulla, autonomic ganglia, and several structures of the brain including the medial habenula, the interpeduncular nucleus, and the inferior colliculus (Gotti et al., 2006). Variations in *CHRNB4* and *CHRNA3*, particularly SNPs between the coding regions, have been associated with age of onset for both tobacco and alcohol, suggesting a possible role of these genes in a more general behavioral disinhibition phenotype (Schlaepfer et al., 2008). *CHRNA3* and *CHRNA5* have also been associated with risk for early pleasurable response to nicotine for heavy smoking (Berrettini et al., 2008), nicotine dependence (Bierut et al., 2007; Saccone et al., in press; Saccone et al., 2007; Thorgeirsson et al., 2008), and lung cancer (Amos et al., 2008; Hung et al., 2008). Interestingly, the risk allele for nicotine dependence was found to be protective against cocaine dependence (Grucza et al., 2008). Given what is already known about the complexity of gene regulation in this cluster of genes (Deneris, Boulter, Swanson, Patrick, & Heinemann, 1989; McDonough et al., 1997; Xu et al., 2006), as well as the complexity of nicotinic receptor subunit protein regulation and localization (Gotti et al., 2007), there are likely many different variations in this chromosomal region contributing to a variety of drug-related behaviors with unique effects.

Receptors containing α2 are generally found in the retina and in the interpeduncular nucleus (IPN). The α7, α8, and α9 subunits form homopentameric (and sometimes heteropentameric) receptors. Receptors composed of α7 or α8 subunits mediate glutamate release, though α8 receptors are rare and have much lower affinity than α7 (Gotti et al., 2006). α7 receptors are highly expressed in the brain, particularly in the cortex, hippocampus, and subcortical limbic regions (Gotti et al., 2007), and

there is good evidence *CHRNA7* is associated with schizophrenia (Gault et al., 2003; Leonard et al., 2002). The *CHRNA7* gene was reported to be associated with nicotine dependence among Israeli females (Greenbaum et al., 2006), but other studies have not found evidence for this (Bierut et al., 2007; Saccone et al., 2007). Few studies have examined *CHRNA2*, *CHRNA9*, *CHRNA8*, and *CHRNA10*. Those that have were large candidate gene studies and genome-wide associations and have found little evidence for association of polymorphisms in these receptor subunits or measurable changes in smoking or alcohol behavior (Berrettini et al., 2008; Greenbaum et al., 2006).

Summary

In review, numerous candidate genes have been examined for association with alcohol, tobacco, and related behaviors. In many cases, some studies find evidence for association, while others do not. It is difficult to compare across studies which differ on several levels: subject ascertainment (ethnicity, clinical/control status), sample size (family-based or cases and controls), phenotypic assessment (diagnostic criteria, quantity/frequency measures), and polymorphisms assessed (specific number and distribution of SNPs). Some of the most convincing genes to emerge include the alcohol and aldehyde dehydrogenase genes, the *GABRA2* genes, and several of the nicotinic receptor genes. Given the complexity of substance use disorders and of neuronal systems, future work examining possible gene × gene interactions may yield additional insight into the underlying physiological mechanisms. Investigators are just beginning to attain sample sizes and methodological approaches that are capable of testing for gene × gene interactions. These developments, in addition to work examining gene × environment interaction, will be an exciting area of innovation. Such discoveries should yield important knowledge about how different genetic interactions combine with environmental factors to contribute to increased risk for these disorders, providing new opportunities for prevention and treatment in children and their families.

PROMISE OF FUTURE GENETIC FINDINGS

These genetic studies raise an important question: How might future and current genetic findings be used, and how will those uses impact individuals, families, and society? Although the ability to forecast all such uses and implications is impossible, thoughtful consideration is merited, especially given that these disorders can carry substantial social stigma.

Treatment Implications

Given the serious implications of these disorders for individuals and their families (briefly outlined in the Introduction), a hope to prevent and effectively treat these disorders is understandable. Currently, only

three medications are FDA approved for the treatment of alcohol dependence in the USA: (1) disulfiram, (2) naltrexone, and (3) acamprosate (Williams, 2005). Three are also approved for the treatment of nicotine dependence: (1) nicotine replacement, (2) bupropion, and (3) varenicline (Le Foll & George, 2007). No medications are approved for the treatment of methamphetamine, cocaine, inhalant, cannabis, or hallucinogen dependence and none are approved for the treatment of conduct disorder and antisocial personality disorder. Identifying genetic contributors for liability to these disorders could provide an important understanding of underlying biological processes and provide logical drug targets for treatment. Advances in the pharmacological treatment of substance use disorders could potentially result in the migration of the primary treatment for substance dependence from specialists and specialty clinics to the offices of family practitioners.

Current work already makes use of our genetic understanding of alcoholism and molecular advances for treatment development. For example, it has long been known that a SNP common in east Asians in the aldehyde dehydrogenase gene inactivates that enzyme (section "Linkage Approach"), leading to an uncomfortable reaction to alcohol consumption (i.e., facial flushing and nausea) and reducing the risk for alcohol dependence, especially among those homozygous for the SNP. Disulfiram also acts on this enzyme but nonadherence with that medication sometimes limits the clinical effectiveness, and efforts to develop longer acting preparations or implants have not yet been fully successful. Recent research addresses this problem through a genetic approach by injecting an adenoviral vector containing an antisense *ALDH2* gene. That adenovirus then produces antisense RNA which markedly reduces aldehyde dehydrogenase activity in animal models (Ocaranza et al., 2008). If someday proven safe and effective in humans, approaches such as this might also be incorporated into the treatment for patients with alcohol and other substance dependence.

Genetic findings may help not only in the development of new treatment strategies but also in matching available treatments to patients. Such an approach assumes that inherited differences in drug metabolism and drug targets have important effects on treatment toxicity and efficacy (Welton, Johnstone, David, & Munafo, 2008). There is mounting evidence that as expected, response to medical treatment is affected by the particular genetic variants a person carries. For example, although preliminary, recent work has suggested that a functional genetic polymorphism in the *OPRM1* gene might predict naltrexone response in alcohol-dependent patients (Anton et al., 2008). Furthermore, variations in the *DRD2* and *DBH* genes have also been associated with response to nicotine replacement therapy and bupropion, with carriers of the *DRD2* A1(T) allele responding better to bupropion and those with the A2(C) allele and/or *DBH* 1368A responding to nicotine replacement (Welton et al., 2008). Recently the willingness of physicians to use genetic tests to tailor treatment was examined. These studies suggest that physicians are amenable to such "pharmacogenetic" approaches to therapy, particularly if the tests did not also indicate risk for other psychiatric disorders (such as the association of *DRD2* and *DBH* with general drug addiction and

neuropsychiatric disorders) (Shields et al., 2008). From a practical clinical standpoint, examinations of the cost-effectiveness of tailoring treatment to genotype are mixed (Heitjan et al., 2008), but costs are decreasing and timely success of treatment is a clinical priority. Such work suggests the possibility of a day when physicians might target pharmacological treatment for substance use disorders based in part on the genetic constitution of individual patients.

Prevention/Genetic Susceptibility Testing

It is important to underscore that although about half of the population variance for substance use disorders appears to be explained by genetics, we currently have identified only a handful of supportable genetic risk factors. As with most complex traits, there are likely many genes which each contribute only a small amount to the population variance. Therefore, a careful family history is likely to provide more predictive validity for substance use disorder risk than any single genetic risk factor at this time (excluding individuals homozygous for ALDH2*2). Still the promise of genetic research is that we can identify many between-individual genetic differences that contribute to the liability to substance use disorders and collectively those genetic polymorphisms will provide highly meaningful information.

Once identified, genetic susceptibility testing is another somewhat more controversial emerging application of genomics. Recent studies suggest that the majority of adolescents (>60%) and adolescent medical providers (61–70%) are willing to utilize genetic tests for risk of nicotine addiction, particularly in the presence of preexisting conditions (O'Neill et al., 2008). However, the hope that such individual-specific genetic knowledge will help with prevention is tempered by the fact that only 30–44% of adolescents reported that knowing their genetic risk would influence their smoking behavior (Tercyak, Peshkin, Wine, & Walker, 2006). This is consistent with what has been observed in medically at-risk children, who show similar rates of smoking compared to their peers, despite knowing that their health status makes them more susceptible to the negative consequences of smoking (Tercyak, Britto, Hanna, Hollen, & Hudson, 2008). However, evidence that the general public will be interested in such approaches is supported by the success of companies such as 23andme, which offer genetic testing via mail for a number of health traits and diseases for a relatively low cost (www.23andme.com). Clearly, additional research is needed to determine which approaches might be most effective for integrating genetic data at the level of prevention in adolescents.

Another important ethical issue to consider in the family context is that genes are inherited, so an individual's test results also reflect probabilities of carrier status in family members. In some cases, individual genes have been associated with a relatively broad spectrum of related disorders, which may carry different levels of social stigma (Shields, Lerman, & Sullivan, 2004). For example, many of the genetic variants associated with nicotine dependence (a somewhat "accepted" behavior) have

also been shown to be risk factors for more general addictive behaviors, schizophrenia, depression, and other neuropsychiatric conditions. Thus the pleiotropic nature of these genes adds a level of complexity that must be carefully counseled and appropriately informed if genetic testing becomes more common.

Unintended Consequences

The push to find between-individual genetic contributors to risk for tobacco and alcohol dependence may have important implications for treatment and prevention and also might relieve terrible suffering within families, but there are also some potential unintended consequences. For example, such genetic advances may lead to stigmatization of individuals or the public may misunderstand the implications of those findings. If highly effective treatments can be found, adolescent patients and their parents might disagree on whether to pursue such treatment, and given the high costs to society from these disorders, the potential for enforced therapy through the legal system is also of concern (Coors & Raymond, 2009).

CONCLUSION

In conclusion, tobacco and alcohol use and associated risk behaviors lead to serious detrimental consequences in children and their families, as well as create a heavy burden on society. There is strong evidence that common genetic factors play a role in mediating the comorbidity of these behaviors and are likely to interact in complex ways with environmental components to affect overall risk. A number of human genetics studies have identified genes that are likely to contribute to alcohol and tobacco phenotypes. In addition, strong evidence is emerging for several candidate genes which may play a role in mediating initiation, early subjective response, quantity and frequency of use, and abuse and dependence of these drugs. These include the alcohol and aldehyde dehydrogenase genes associated with protection against alcoholism as well as neuronal genes such as the $GABA_{A2}$ receptor (*GABRA2*) and the cluster of nicotinic receptor subunit genes (*CHRNA5/A3/B4*). The recent advent of high-throughput genotyping methods, combined with concurrent development of advanced statistical tools to analyze such data, promises continued identification of new genes and mechanisms which contribute to these disorders. Future studies focused on gene–gene interactions and gene–environment interactions have the promise to yield new insight into the complex interactions between genes and environment. Such knowledge is anticipated to aid in prevention and treatments that are uniquely targeted at an individual's genetic predisposition. Along with this burgeoning wealth of information, it will be critical for geneticists to develop outreach programs to educate the general public about how to interpret personalized risk factors. It will be important to establish close collaborative efforts between the basic scientists who study the underlying

molecular genetic mechanisms and the clinicians who serve children, adolescents, and their families to ensure the best possible integration of new knowledge and technology into their health practices.

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Childhood Neuropsychiatric Risk

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INTRODUCTION

Neuropsychiatric disorders affecting children, such as attention deficit, hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), schizophrenia, and autism are considered familial with estimated heritability rates of 75, 78, 84, and 93%, respectively (Tsuang, Glatt, & Faraone, 2006), suggesting that genes confer the major risk susceptibility.

Identifying the underlying genes, however, is proving challenging. In part this is due to the heterogeneous clinical presentation of these disorders that complicate phenotype ascertainment, as well as the complex genetic underpinnings, which may explain why these disorders were not accessible by traditional genetic methods.

Recent advances in genotyping technology, sophisticated computational techniques, mapping of the human genome, and more recently the HapMap are permitting linkage and association studies that hold promise for neuropsychiatric disorders with complex underlying genetic risks. At this time, genes conferring major risks have not been detected, but rather candidate genes conferring a small amount of risk have been identified for all of these disorders, suggesting that multiple genes are likely to be involved and possibly the same gene may result in different phenotypes. Genetic studies that include children have advantages over those conducted in adults, in that parents are more likely to be available and thus provide data for association studies that avoid issues with genetic stratification. However, they are also more complex since phenotypes may change and confound studies that include all developmental stages.

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Gene discovery for neuropsychiatric disorders holds promise for advancing the understanding of pathophysiology, the development of diagnostic testing, pharmacotherapy based on the individual's molecular pathology and liver metabolic capacity, as well as potential cures. These important advances will also bring personal and ethical considerations for families faced with decisions of risk assessment and potential discrimination. In this chapter we will review the literature on several neuropsychiatric disorders with special emphasis on disorders primarily occurring during childhood and their potential impact on individuals and families. Literature searches were performed to identify published articles dealing with genetics and neuropsychiatric disorders. Search terms used included attention deficit, hyperactivity disorder, obsessive-compulsive disorder, schizophrenia, autism, genetics, environmental interactions, pharmacogenetic, genetic testing, genetic counseling, genetic ethics, copy number variations.

BACKGROUND AND SIGNIFICANCE

Although neuropsychiatric symptoms occur in autosomal dominant, recessive, and X-linked disorders, common neuropsychiatric disorders such as ADHD, OCD, schizophrenia, and autism are multifactorial. Familial aggregation observed in neuropsychiatric disorders such as ADHD, OCD, schizophrenia, and autism was followed by twin studies that showed significant heritability (Bailey et al., 1995; Carey & Gottsman, 1981; Faraone et al., 2005). Classical segregation analysis which assumes etiologic homogeneity has not been successfully applied to neuropsychiatric disorders since different genes may segregate in different families that in turn may be exposed to different environmental factors. For example, although segregation analysis implicates a major locus for OCD, transmission has been difficult to model (Alsobrook, Leckman, Goodman, Rasmussen, & Pauls, 1999; Cavallini, Bertelli, Chiapparino, Riboldi, & Bellodi, 2000; Hanna, Fingerlin, Himle, & Boehnke, 2005a; Nestadt et al., 2000a). Linkage analysis (a DNA marker with a known chromosomal localization congregates with a disease in families) has also proved to have limited success in the search for susceptibility genes.

Currently, the major approach in identifying susceptibility genes has been the association study. Designs that make use of unrelated cases and controls are popular because of their efficiency and the ease of recruiting subjects; however, these are limited by population stratification that can lead to spurious associations (i.e., the existence of genetically different sub-groups in the population under study). In contrast, family-based association studies are known to be unaffected by the presence of population stratification and can be used as an alternative to case–control studies when relatives of cases are available (Zhao, 2000). These are best done in children since it requires the frequency of transmission versus non-transmission of marker alleles from heterozygous parents to the affected offspring (Spielman, McGinnis, & Ewens, 1993). The

availability of parental genotypes also allows testing of specific hypotheses such as parent of origin effects that cannot be tested in case–control samples.

In addition to single nucleotide variations, larger and more complex variations have been recently identified in the human genome, referred to as copy number variation (CNVs) (Eichler, 2006; Sharp et al., 2006). These duplications and deletions can result in changes in gene dosage that may contribute to genomic instability (Emanuel & Shaikh, 2001) and phenotypic variations (Iafrate et al., 2004; Sebat et al., 2004) in complex disorders. Investigation of CNVs in neuropsychiatric disorders is just beginning, and preliminary studies in schizophrenia and ADHD (Elia et al., 2009) suggest that multiple individually rare mutations impacting genes involved in neurodevelopmental pathways may be playing a role (Walsh et al., 2008).

Conducting genetic studies in children provides some advantages such as the possibility of greater genetic risk with childhood onset for disorders such as schizophrenia where childhood onset, although rarer, is considered to potentially have greater genetic liability (Rapoport, Addington, Frangou, & Psych, 2005; Walsh et al., 2008). Childhood studies also pose challenges such as changing phenotype that may be reflective of varying gene expression throughout development. Neurotransmitter ontogeny studies indicate developmental changes in some of the major neurotransmitter pathways. For example, dopamine activity appears to decrease as the organism matures. Brains of children release more homovanyllic acid (HVA) into blood than do brains of adults (Fryo, Settergre, & Sedvall, 1978), and cerebral spinal fluid (CSF) HVA concentrations were found to decrease with age in children and adults with neuropsychiatric disorders (Cohen et al., 1974; Leckman et al., 1980; Seifert, Foxx, & Butler, 1980). Norepinephrine appears to increase with maturation, and serum dopamine beta-hydroxylase (DβH) increases with age especially during the first few years after birth (Freedman et al., 1972; Weinshilboum, 1979). The development of the serotonergic system is unclear. Whole-blood serotonin levels decrease over childhood and adolescence (Ritvo et al., 1971); however, CSF 5-HIIA concentrations are stable throughout the life cycle (Leckman et al., 1980; Shaywitz, Cohen, Leckman, Young, & Bowers, 1980), but one study did report a reduction in this metabolite with age (Seifert et al., 1980). No relationship has been reported between age and 5-HIAA or serotonin in human brain autopsy tissue (Gottfries, Roos, & Winblad, 1974). Serotonergic innervation of the cortex does not appear to change after fetal life, and 5-HT1A receptors remain stable after term age in all parts of the brain except the cerebellum where they are present at high levels at term age and then decrease gradually to very low doses in adulthood (del Olmo et al., 1998). These findings suggest that genetic association studies may need to consider developmental stages. In addition, gene expression studies during different developmental stages may also be necessary in order to determine the actual effect of the variants that are found to be important.

Combined recruitment efforts and sharing of data are also important since large samples will be required to identify and validate variants. This is being achieved through several groups including the OCD Collaborative Genetic Study, the ADHD Molecular Genetics Network, the Autism Genetic Resource Exchange (AGRE), the International Genetic Study of Autism Consortium (IMGSAC), and the Psychiatric GAIN Consortium (PGC), as well as others.

While recent technology is allowing advances in genetics to move at high velocity, investigation in the handling and managing of the acquired knowledge is lagging. For neuropsychiatric disorders, the impact on the individual and society of this new information is not well understood. Research addressing the psychosocial impact and how this is handled is needed.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders with an estimated worldwide pooled prevalence of 5.29% in school-aged children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007a). ADHD is characterized by developmentally inappropriate levels of hyperactivity, impulsivity, and inattention, as well as executive function deficits leading to significant learning, behavioral, and social impairments (Faraone et al., 1996; Foley et al., 1996; Greenfield et al., 1988; Nigg et al., 2005).

Family Studies

A higher risk for ADHD has been reported in siblings of ADHD probands (20.8% versus 5.6% in controls) (Biederman et al., 1992), among first-degree family members of ADHD male (Lombroso, Pauls, & Leckman, 1994) and female probands (Faraone et al., 1995; Faraone, Biederman, Keenan, & Tsuang, 1991), and in second-degree relatives (Faraone, Biederman, & Milberger, 1994). Shared genes rather than shared environment were suggested to be responsible for the increased familial aggregation by adoption studies reporting 18% ADHD in biological versus 6% in adoptive parents (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). Twin studies with heritability estimates of 51–90% also indicate a high genetic contribution to phenotypic variation (Faraone et al., 2005) that appears to remain stable over time (Bergen, Gardner, & Kendler, 2007).

Candidate Genes

Although ADHD has been reported to occur in single gene disorders such as Huntington's, Marfan's, neurofibromatosis, thyroid receptor B gene, and fragile X, X-linked adrenoleukodystrophy, the common form of ADHD is considered for the most part to be caused by many different genes working together conferring risk or protection.

Candidate genes encoding proteins involved in neurotransmission have been preferentially explored. Initially, the focus centered on genes relevant to dopaminergic neurotransmission based on neuroimaging studies, animal models, and behavioral improvement from dopaminergic agents. The search has been extended to include other major neurotransmitters (noradrenergic, serotonergic, glutaminergic, cholinergic) and confirmed association has been reported for *DAT1, DRD4, SNAP-25, DRD5, DAT1, SNAP25, 5HTT, HTR1B*, and *DBH*. However, these candidate genes confer relatively small risk (OR 1.24–1.45) (Mick & Faraone, 2008). Support is emerging for combination of polymorphic alleles, or haplotypes as significant risk factors including *DAT1* (Asherson et al., 2007; Brookes et al., 2006b), *DRD4* (Kereszturi et al., 2007), *BDNF* (Xu et al., 2007), *5HTT* (Li et al., 2007), *HTR2C* (Li et al., 2006), *ADRA2A* (Deupree et al., 2006). High-density tagSNPs genotyping has provided support for variants in these genes as well as others (Brookes et al., 2006a).

Genomic Studies

Genome-wide linkage studies have not identified any significant variant; however, several chromosomal regions with potential linkage have been identified, some overlapping in two or more studies including 5p, 6q, 7p, 11q, 12q, and 17p (Arcos-Burgos et al., 2004; Bakker et al., 2003; Fischer, Barkley, Smallish, & Fletcher, 2002; Ogdie et al., 2004, 2003; Smalley et al., 2002). In particular, a pooled analysis of the US and Dutch data identified a single region of overlap at 5p13 (Ogdie et al., 2006). However, the disease contributing genes in these locations remain to be identified. A family-based association study (Neale et al., 2008) as well as our own study (unpublished results) have not identified any variant with genome-wide significance, and this is most likely due to the fact that very large samples are required to find genes that confer a very small amount of risk. In the first CNV study reported in ADHD, an enrichment of rare structural variants were found in genes involved in neurodevelopmental pathways suggesting that ADHD may be due to rare variants rather than common genes (Elia et al., 2009).

Gene–Environmental Interactions

ADHD has been associated with low birth weight (Breslau & Chilcoat, 2000; Szatmari, Saigal, Rosenbaum, Campbell, & King, 1990). Lower birth weight has also been associated with ADHD in monozygotic (MZ) birth weight-discordant twin pairs (Asbury, Dunn, & Plomin, 2006; Lehn et al., 2007; Sharp et al., 2003). Higher ADHD ratings were found in the lighter pair of MZ and dizygotic (DZ) twins in birth weight-discordant pairs; this outcome has been attributed primarily to environmental factors (Hultman et al., 2007).

Maternal smoking during pregnancy has been associated with ADHD in some studies (Braun, Kahn, Froehlich, Auinger, & Lanphear, 2006; Huizink & Mulder, 2006; Kotimaa et al., 2003; Langley, Rice, van den Bree, & Thapar, 2005; Linnet et al., 2005; Mick, Biederman, Prince,

Fischer, & Faraone, 2002), although to a lesser degree when genetic risk is controlled for (Knopik et al., 2005). Comorbid conditions may play a role here since prenatal nicotine exposure has also been associated with ODD and CD (Day, Richardson, Goldschmidt, & Cornelius, 2000; Huizink & Mulder, 2006; Maughan, Taylor, Caspi, & Moffitt, 2004; Orlebeke, Knol, & Verhulst, 1999; Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002). A longitudinal study that considered potential overlapping factors and included low birth weight and normal birth weight children found that prenatal maternal smoking was strongly linked to ODD and CD, independent of birth weight, and not to ADHD. Only low birth weight was associated with ADHD. Maternal smoking was also confounded by maternal drug abuse and educational level (Nigg & Breslau, 2007).

Although gestational alcohol exposure has also been associated with ADHD (Bhatara, Loudenberg, & Ellis, 2006; Fryer, McGee, Matt, Riley, & Mattson, 2007), twin studies do not confirm this association (Neuman et al., 2007). Offspring of female MZand DZ twins were concordant or discordant with alcohol use as parents were found to be at a higher risk of having ADHD than controls (Knopik et al., 2006). A pilot study reporting higher risk of ADHD in children with parents with substance use disorder (alcohol and other substances) did not control for CD or other comorbidities (Wilens et al., 2005).

Additional environmental risk factors associated with ADHD include emotional distress or family adversity during pregnancy and early in life (Bradley & Golden, 2001; Rodriguez & Bohlin, 2005), prematurity (Bhutta et al., 2002), young maternal age, and bleeding during pregnancy (Milberger, Biederman, Faraone, Guite, & Tsuang, 1997), breech presentation (Sharp et al., 2003), neonatal complications (hospital admission, incubator use, oxygen therapy, general anesthesia, surgery) (Ben Amor et al., 2005), hypoxemia (Bass et al., 2004), encephalitis (Strother, 1973), trauma (Max et al., 1998), lead exposure (Braun et al., 2006), mercury (Cheuk & Wong, 2006), and brain injury from metabolic disorders (Arnold, Vladutiu, Orlowski, Blakely, & DeLuca, 2004a).

At this time there are a few studies investigating gene–environment interactions. In one study, ADHD children with low birth rate that carried the Val variant of the *COMT* gene were at higher risk of developing conduct disorder (Thapar et al., 2005); however, this was not replicated in a separate study (Sengupta et al., 2006). In a 2006 study (Brookes et al., 2006b) where 28.6% of mothers smoked cigarettes (approximately 3 months during gestation) and 57.8% drank alcohol at some time during pregnancy, a significant interaction was found for the 10/3 haplotype encompassing the *DAT* gene for maternal alcohol use while no interaction with genotype was observed for maternal smoking. Kahn and colleagues reported that children homozygous at *DAT* 480/480 genotype and also exposed to nicotine in utero had higher parental ratings on measures of hyperactivity–impulsivity and oppositional behaviors (Kahn, Khoury, Nichols, & Lanphear, 2003). In a study of twin pairs, 24% of mothers reported smoking during pregnancy, and offspring exposed to prenatal nicotine had higher numbers of ADHD symptoms than those not exposed. Risk for ADHD was greater in twins with *DAT* 440 allele exposed to in

utero nicotine than twins that had neither risk factor while no significant interaction was found for *DAT* 480. Risk was also greater with *DRD4* 7-repeat (Neuman et al., 2007) and prenatal nicotine exposure as well as with *CHRNA4* variants (Todd & Neuman, 2007); however, gestational age and birth weights were not accounted for in this study. Psychosocial adversity in adolescents homozygous for *DAT* 480 was found to result in greater ADHD symptoms than in adolescents with other genotypes or with more favorable environments (Laucht et al., 2007).

Investigating environmental–gene interactions is complicated by numerous confounding effects. For example, use of tobacco by pregnant women is independently linked to other factors that could potentially confer risk such as lower birth weight (Secker-Walker, Vacek, Flynn, & Mead, 1997), stress (Rodriguez & Bohlin, 2005), premature rupture of membranes, and placental abruption (Andres & Day, 2000). Regular smoking is also more prevalent in women alcoholics who are also more likely to smoke during pregnancy (Knopik et al., 2006, 2005). Comorbidity also needs to be accounted for given that the environmental risk may be conferred through the comorbid condition and not necessarily through ADHD. Study methodology is also important (Mattson, Calarco, Chambers, & Jones, 2002).

ADHD: Developmental Phenotype

Comorbid disorders, including oppositional defiant disorder (35%), conduct disorder (30–50%), anxiety disorders (25%), mood disorders (15–75%), and learning disabilities (25%) have been reported in clinical samples of ADHD children and adolescents (Biederman, Newcorn, & Sprich, 1991; Brown et al., 2001; Cantwell, 1996; Hinshaw, 1992; Jensen, Martin, & Cantwell, 1997; Spencer, 2006). Higher rates of antisocial behaviors, substance use, and depression are reported in parents of children with ADHD+ODD/CD than ADHD alone (Faraone, Biederman, Jetton, & Tsuang, 1997). It is not known if these associated conditions modify the ADHD phenotype or whether single genes influence multiple phenotypic traits as is suggested in a study by Jain and colleagues where ADHD was found to co-segregate with ODD and CD (Jain et al., 2006). *DRD4* 7R has been reported to be preferentially transmitted to children with ADHD and comorbid ODD (Kirley et al., 2004). Two epidemiological twin studies of adolescents indicate shared as well as unique genetic influence among ADHD, ODD, and CD (Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Nadder, Rutter, Silberg, Maes, & Eaves, 2002). Genetic contribution to comorbid persistence or remission is also important and in an 8-year longitudinal study of ADHD children (ages 4–6 at baseline) subjects with more copies of *DAT* 10R and *DAT* 9R had significantly fewer ODD symptoms over time (Lee et al., 2007).

Pharmacogenetics

Pharmacogenetic studies may provide complementary approaches in the search for biologically relevant disease genes. In ADHD, earlier human

studies, focusing primarily on (DAT1) variants, reported mixed results, attributed to small sample size, lack of controls, randomization, and optimal medication titration (Cheon, Kim, & Cho, 2007; Hamarman, Fossella, Ulger, Brimacombe, & Dermody, 2004; Kirley et al., 2003; Lott, Kim, Cook, & de Wit, 2005; Stein et al., 2005; van der Meulen et al., 2005; Winsberg & Comings, 1999). Two recent well-controlled studies, albeit with small samples, one in preschoolers (McGough et al., 2006) and one in adults (Mick, Biederman, Spencer, Faraone, & Sklar, 2006) and a well-powered study using retrospective parental recall of methylphenidate response (Tharoor, Lobos, Todd, & Reiersen, 2007) also failed to find any association. However, a 2-week crossover study of methylphenidate and placebo, in three groups of children separated by genotype, reported a significant positive response with 9/10 and 10/10 in contrast to the 9 homozygous (Joober et al., 2007). The DAT10R heterozygous genotype has also been associated with positive methylphenidate response in adults (Kooij et al., 2007) and in a study measuring cortical inhibition that also included atomoxetine (Gilbert et al., 2006).

Animal models such as the *DAT1* knockout mouse, which remains responsive to methylphenidate in spite of the lack of a dopamine transporter (Gainetdinov et al., 1999), and the spontaneously hyperactive rat model where reduced α2 adrenoceptor-mediated inhibition of NE release mediates hyperactivity (Russell, Allie, & Wiggins, 2000) have pointed to a noradrenergic focus that has been bolstered by efficacy of selective norepinephrine transporter (NET) inhibitor, atomoxetine, shown to be effective in human ADHD studies (Michelson et al., 2002; Spencer et al., 2002). A significant association has been reported between methylphenidate response and the G allele of *ADRA2A*-1291C>G (da Silva et al., 2008; Polanczyk et al., 2007b) and *NET* G1287A (Yang, Wang, Li, & Faraone, 2004) while an intronic SNP rs47958 and the GCC haplotype were associated with positive mood with amphetamine response in a group of healthy volunteers (Dlugos et al., 2007). The coloboma mouse, where *SNAP-25* is deleted, does not respond to methylphenidate but responds to amphetamine and this effect has been shown to be mediated through D2 dopamine receptors (Fan & Hess, 2007). Hyperactivity in this mouse model is also mediated through α2C-adrenergic receptors (Bruno & Hess, 2006) suggesting that both noradrenergic and dopaminergic systems may be involved. In the only human pharmacogenetic study investigating *SNAP-25*, McGough and colleagues reported improved dose–response with methylphenidate for the T allele compared with the less common G allele for *SNAP-25* T1065G and a negative response for the T allele of T1069C (McGough et al., 2006).

Genetic variants that influence the pharmacokinetics of ADHD medications are also being identified. A gene variant for caboxylesterase 1, the enzyme used to esterify methylphenidate to D, L-ritalinic acid and L-ethylphenidate, has been reported in one subject identified as a poor methylphenidate metabolizer (Patrick et al., 2007). Amphetamine compounds are metabolized through the hepatic CYP450, primarily through *CYP3A4* and to a lesser extent through *CYP2D6* (Markowitz & Patrick, 2001) while atomoxetine is metabolized primarily through *CYP2D6* and

poor metabolizers were shown to have greater symptom improvement (Michelson et al., 2007). At this time tests for genetic variants that influence pharmacokinetics of several psychotropics are available and include analyses for gene variants of *CYP450* such as *2D6* and *2C19.* However, these are not currently being used in the clinical management of ADHD.

Summary and Psychosocial Implications

ADHD is highly heritable with a complex genotype and phenotype. It is likely that there are many genes and environmental factors that confer risk and protection for this disorder. The varying phenotype at different developmental stages also suggests that factors involved in gene expression are most likely playing a role. At this time, ADHD families are not generally provided with or referred for genetic counseling. Currently, there are also no genetic tests available that would provide any clinically useful diagnostic or treatment information. As can be attested by the numerous genetic studies conducted worldwide (Mick & Faraone, 2008), subjects with ADHD and their families are willing to participate in genetic studies. Stigma may be less of an issue for ADHD than for some of the other neuropsychiatric disorders. This may be possibly due to the high prevalence rate and available treatments that are provided in primary care settings.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-compulsive disorder (OCD), characterized by recurrent and intrusive thoughts (obsessions) and repetitive behaviors (compulsions), has an estimated prevalence rate of 1–3% worldwide (Rasmussen & Eisen, 1994).

Family Studies

There is a significant familial aggregation (Nestadt et al., 2000b; Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995) and high monozygotic twin concordance rates (80–87%) (Carey & Gottsman, 1981; Inouye, 1965). Five complex segregation analyses had implicated a major locus with OCD (Alsobrook et al., 1999; Cavallini et al., 2000; Cavallini, Pasquale, Bellodi, & Smeraldi, 1999; Hanna et al., 2005a; Nestadt et al., 2000a); however, the mode of transmission has been difficult to model.

Candidate Genes

Candidate genes involved in serotonergic neurotransmission have been the most widely studied due to the efficacy of serotonin re-uptake inhibitors (SSRIs) in the treatment of OCD, as well as the exacerbation of symptoms by *m*-chlorophenylpiperazine (m-CPP), a serotonin agonist (Pigott et al., 1991). As reviewed by Kim and Kim (Kim & Kim, 2006) and Hemmings and Stein (Hemmings & Stein, 2006) results have been mixed for serotonin transporter (*5-HTT*) and serotonin receptor genes variants

(*5-HT2A, 5-HT2C,* and *5-HT1Dβ*). Negative results have also been reported in association studies for variants of tryptophan hydroxylase (*TPH*) except for early-onset OCD. Dopamine transporter (*DAT1*) and dopamine receptor gene variants (*DRD2, DRD3*) do not appear to confer risk for OCD while a *DRD4 VNTR* variant may possibly confer a protective effect, while results for MAO and COMT gene variants are mixed (Hemmings & Stein, 2006; Kim & Kim, 2006).

OCD is clinically heterogeneous with considerable variability in the types of obsessions and compulsions (Mataix-Cols, Rosario-Campos, & Leckman, 2005) as well as clinical course and treatment response (Miguel et al., 2005). These clinical differences that may potentially reflect different genetic signatures have been difficult to consider due to the limited sample sizes. However, combined recruitmentefforts such as the OCD Collaborative Genetic Study are making these feasible, and in 219 multiplex OCD families where compulsive hoarding was treated as a specific phenotype, a suggestive linkage to chromosome 14 marker (D14S588) is found. In families with two or more hoarding relatives, significant linkage was also found for a chromosome 14 marker (C14S1937) (Samuels et al., 2007).

Genomic Studies

The first genome-wide scan study, where phenotype was ascertained through pediatric probands, a region of suggestive linkage was found in chromosome 9p24 (Hanna et al., 2002). This finding has been subsequently replicated in another study (Willour et al., 2004). This region contains the gene encoding the neuronal glutamate transporter, *SLC1A1.* Although no association was found between *SLC1A1* in a small OCD cohort (Veenstra-VanderWeele et al., 2001), a modest association was reported between two microsatellite markers flanking *SLC1A1, GATA62F3*, and D9S288 by Willour (Willour et al., 2004) and in two variants (rs301434 and rs 301435), located within a single haplotype block in male but not female offspring (Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006). Further support for glutaminergic neurotransmission involvement in OCD comes from positive studies for two ionotropic glutamate receptor genes, the *N*-methyl-D aspartate subunit 2B gene (*GRIN2B*) (Arnold et al., 2004b) and the kainite receptor 2 gene (*GRIK2*) (Delorme et al., 2004).

Gene–Environmental Interactions

Heritability studies in OCD also indicate that environmental factors are also important. However, these have not yet been deciphered. In a recent study, childhood physical neglect and the S/S genotype of the serotonin transporter (*5-HTT*) gene have been reported to predict dissociation in patients with OCD (Lochner et al., 2007).

OCD Developmental Phenotype

Early-onset OCD has been reported to be highly familial, with significantly higher rates occurring in first-degree relatives of early-onset OCD subjects versus first-degree relatives of later-onset subjects (Hanna, Fischer, Chadha, Himle, & Van Etten, 2005b). OCD genetic studies that included children have reported an association between –1438A allele of *5-HT2A* (Meira-Lima et al., 2004) and a separate study reported a significant overtransmission of the C allele of SNP rs4565946 of *TPH2* with early-onset OCD (Mossner et al., 2006). A more recent study found evidence for linkage on chromosome 3q27–28 with a possible role of genes on chromosome 1 for earlier-onset OCD (Shugart et al., 2006).

Pharmacogenetics

Effective medications for OCD include the serotonin reuptake inhibitors (SSRIs). These medications, in particular fluoxetene, paroxetine, and to a lesser extent sertraline, inhibit 2PD6 (Richelson, 1997). As summarized by Flockhart and Oesterheld (2000), there is a large interindividual variability in CYP drug interactions which can result from numerous factors including the amount of drug present, its affinity for a CYP, the involvement of multiple CYP pathways, the amount and activity of the CYP (e.g., CYP3A is more abundant than CYP2C9), gender (women have higher CYP3A efficiency), diet, personal habits (smoking), and genetic variation. In addition, CYP efficiency varies during development. By age 1, CYP activity is 40% of adult levels (Cresteil T). CYP2D6 reaches 50% of adult capacity by the first month of life but a large interindividual variability has been noted (Jacqz-Aigrain et al., 1992; Treluyer et al., 1991). Overall CYPs are more efficient during childhood, declining to adult levels after puberty (Oesterheld, 1998), and resulting in higher dose requirements of medications for children compared with adults.

Summary and Psychosocial Implications

Glutaminergic gene variants appear to be the most promising for OCD while evidence for serotonergic and some dopaminergic genes is mixed. Larger and more homogenous cohorts that include subjects with early-onset will be important in future studies. There are currently no studies on genetic counseling for families with OCD. Information regarding the CYP polymorphisms may be helpful to families/individuals considering treatment with SSRIs.

SCHIZOPHRENIA

Schizophrenia is a severe brain disorder affecting 1% of the population and manifesting with delusions, auditory hallucinations, disorganized speech and thinking, negative symptoms consisting of apathy, lack of

motivation, blunted affect, affective flattening, memory and executive function deficits (American Psychiatric Association[APA], 2004).

Family Studies

Schizophrenia and other spectrum disorders such as schizoaffective disorder, schizotypal disorder, and paranoid personality disorder are reported to be increased in relatives of subjects with schizophrenia (Kendler et al., 1993; Nicolson et al., 2003; Nicolson & Rapoport, 1999). Monozygotic twins have concordance rates of 41–65% (Cardno & Gottesman, 2000).

Although schizophrenia usually emerges in late adolescence and early adulthood (Hafner, Maurer, Loffler, & Riecher-Rossler, 1993), it was described in children since the time of Kraepelin (Adityanjee, Aderibigbe, Theodoridis, & Vieweg, 1999). Controversy over nosological status was reflected in earlier versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) where the "childhood schizophrenia" category included psychotic and autistic disorders (APA, 1968). Landmark studies by Kolvin differentiated childhood schizophrenia from pervasive developmental disorders (Kolvin, Garside, & Kidd, 1971) and more recent studies at the NIMH indicate that it appears to be clinically and biologically similar to the adult form (Nicolson & Rapoport, 1999). Childhood-onset schizophrenia, defined as onset of psychosis by age 12, has similar symptoms as the adult form and in addition these children are also reported to have greater delays in social, motor, and language development (Alaghband-Rad et al., 1995; Hollis, 1995; Nicolson & Rapoport, 1999).

The most consistent brain structural abnormalities reported in schizophrenia include enlarged lateral ventricles and reduced temporal and prefrontal gray matter volumes (Lawrie & Abukmeil, 1998). Longitudinal studies are showing progressive gray matter loss that begins with the early phases of the illness (Pantelis et al., 2005) considered to be due to loss of glia, synaptic and dendritic arbors, and vasculature (Selemon & Goldman-Rakic, 1999). The loss of gray matter in the NIMH childhood-onset schizophrenia cohort followed the same parietal–frontal–temporal progression seen in normal adolescence (Gogtay et al., 2004), but to an exaggerated degree suggesting a loss of control of synaptic pruning. White matter integrity rather than reduction in volume is also reported (Kanaan et al., 2005).

Candidate Genes

Association studies have identified several candidate genes including *DTNBP1, NRG1, RGS4, GRM3, DAOA(G72)* and *DAO, BDNF, DISC1, COMT*, and *PRODH* (Harrison & Weinberger, 2005; Karoutzou, Emrich, & Dietrich, 2008). One of the gene variants with increasing support in schizophrenia susceptibility is neuregulin 1 (*NRG1*) known to influence glutaminergic signaling by regulating the *N*-methyl-D-aspartate (NMDA) receptors (Falls, 2003). It also plays a very important role in oligodendrocyte development, found impaired in null *NRG1* mice (Vartanian, Fischbach, & Miller, 1999),

synaptic remodeling, neuronal migration, and brain development (Tosato, Dazzan, & Collier, 2005). The relationship between polymorphisms in *NRG1* risk alleles and regional brain development throughout adolescence and early adulthood was explored in a cohort of children with schizophrenia that had been recruited and followed at the NIMH. Genotyping results include an association with SNP 8NRG221533, with the same allele as that also reported in a Dutch sample (Bakker et al., 2004) but opposite to the original reported association by Stefansson and colleagues (Stefansson et al., 2002).

In addition to *NRG1*, other genes involved in oligodendrocyte function have been receiving a great deal of attention due to their impact on myelination. Disturbances can impair axonal insulation that may possibly contribute to the transmission of information across brain regions. Axonal insulation is considered strategically important in brain myelination that assures connectivity across brain regions and these disturbances could result in impaired cognitive and experiential abnormalities of schizophrenia (Aston, Jiang, & Sokolov, 2004; Davis et al., 2003; Frith, 1996). Some of these genes include *MAG, MAL, CNP, TF, GSN*, and *ErbB3* (Karoutzou et al., 2008).

Genomic Studies

Chromosomal abnormalities have been reported in adult-onset schizophrenia (Bassett, 1992; DeLisi et al., 1994; Karayiorgou & Gogos, 1997) as well as in childhood-onset schizophrenia (Nicolson et al., 1999; Yan et al., 2000). However, in the NIMH child cohort, all the children with chromosomal abnormalities (one child with XO, one with a balanced translocation of chromosomes 1, and three cases with a 22q11 deletion), also had other risk factors for schizophrenia (Nicolson & Rapoport, 1999). No single gene or genes have been thus far identified as causal for schizophrenia, however, loci at several chromosomes have been reported (1, 2, 4, 5, 6, 7, 8, 9, 10, 13, 15, 22, and X) (Karoutzou et al., 2008; Riley & McGuffin, 2000). Although results of several genome-wide studies were inconsistent, a meta-analysis identified three loci that reached genome-wide significance including 8p, 13q, and 22q (Badner & Gershon, 2002).

Copy number variations in genes affecting neurodevelopmental pathways have also been reported in schizophrenia including deletions disrupting *NRXN1* (Kirov et al., 2008; Walsh et al., 2008), a de novo duplication involving *APBA2* (Kirov et al., 2008), deletions containing *CNTNAP2* (Friedman et al., 2008). In addition, numerous deletions and duplications of various sizes affecting genes in neuregulin, ERK/MAPK, synaptic long-term potentiation, axonal guidance, integrin signaling, and glutamate receptor signaling have also been identified (Walsh et al., 2008). Deletions have also been recently identified in chromosomal regions important for velo-cardio-facial syndrome as well as on 15q13.3 and 1q21.1 (Stefansson et al., 2008; International Schizophrenia Consortium, 2008).

Developmental Phenotype

The different symptoms of schizophrenia are also being attributed to different gene variants. For example, cognitive impairment, a major characteristic of schizophrenia (Weickert et al., 2000), may in part be due to catechol-*O*-methyltransferase (*COMT*) variants. The val$^{108/158}$met polymorphism results in two variants of the enzyme that metabolizes catecholamines. The val form, associated with higher enzyme activity and therefore subsequent lower levels of available synaptic dopamine, has been associated with poorer performance on working memory and executive function tests irrespective of psychiatric diagnoses (Diaz-Asper et al., 2008), and inheritance of one or two val alleles has been reported to slightly increase the risk of developing schizophrenia (Chen et al., 2004; Craddock, Owen, & O'Donovan, 2006; Egan et al., 2001; Fan et al., 2005; Glatt, Faraone, & Tsuang, 2003; Li et al., 1996; Shifman et al., 2002; Wonodi, Stine, Mitchell, Buchanan, & Thaker, 2003). Other single nucleotide polymorphisms (SNPs) across the *COMT* gene have also been associated with the risk of developing schizophrenia (Delorme et al., 2004; Li et al., 2000; Shifman et al., 2002) and these may modulate the val$^{108/158}$met effect. Negative symptoms in schizophrenia have been associated with the methylenetetrahydrofolate reductase (*MTHFR*) 677T variant (Roffman et al., 2008).

Gene–Environmental Interactions

The concordance rate between monozygotic twins is not 100% suggesting that environmental factors influence liability. Furthermore the correlation for age of onset in monozygotic twins concordant for schizophrenia is also less than 1.0 suggesting that non-genetic factors may also play a role in determining the age of onset (Kendler, Karkowski-Shuman, & Walsh, 1996). Some of these factors include severe maternal stress during the first trimester (Khashan et al., 2008) and obstetrical complications that have been associated with an earlier age of onset (O'Callaghan et al., 1992; Verdoux et al., 1997). Infectious agents such as *Toxoplasmagondii* (Niebuhr et al., 2008) have also been associated with schizophrenia while results for influenza A, the most widely studied infectious agent in schizophrenia, are conflictual due to methodological flaws (Brown & Susser, 2002) with a sevenfold increase reported in a well-done study showing a weak association (Brown et al., 2004).

Pharmacogenetics

As summarized by de Leon and colleagues (de Leon, Armstrong, & Cozza, 2006), CYP2D6-poor metabolizers may not tolerate many typical antipsychotics and risperidone and it may be safer to consider treatment with antipsychotics not dependent on CYP2D6 (e.g., clozapine, olanzapine, quetiapine, ziprasidone). CYP2D ultrametabolizers may need higher doses

of typical antipsychotics and risperidone but may respond to usual doses of other antipsychotics.

Summary and Psychosocial Implications

Schizophrenia is thought to result from many genes having a small effect on brain development that are likely to be modified by epigenetic and environmental factors.

Future genetic studies that include brain morphology and the examination of endophenotypes (disease-related phenotypes) such as neurocognitive function (Greenwood et al., 2007) in addition to the clinical phenotypes may have greater success in identifying the corresponding genes. Childhood-onset schizophrenia is rare but widely considered to result from greater genetic liability (Rapoport et al., 2005) and thus potentially very important in the search for the underlying genes.

As reviewed by Lyus (2007), genetic counseling is considered important for patients with schizophrenia and their families. However, in an online survey of patients and relatives of subjects with schizophrenia, only 5% of relatives and none of the subjects had received any counseling (Lyus, 2007).

It is hoped that identifying the underlying genes for schizophrenia will decrease stigma. However, a 2001 population survey indicates a desire for greater social distancing from the individuals depicted as schizophrenic when schizophrenia was attributed to a brain disease and to a lesser degree when it was attributed to heredity (Dietrich, Matschinger, & Angermeyer, 2006).

PERVASIVE DEVELOPMENTAL DISORDERS

Pervasive developmental disorders include autism, Aspergersyndrome, PDD-NOS, Rett syndrome, and childhood disintegrative disorder (APA, 2004). Autism or autistic disorder (AD), first described by Kanner in 1943 (Kanner, 1943), is characterized by qualitative impairment in social interactions and communication as well as restricted repetitive and stereotyped patterns of behaviors with onset prior to age 3. Asperger syndrome (AS) has similar characteristics but cannot have significant delays in the development of language (although the social use of language is typically impaired) nor significant delays in cognitive development. Pervasive developmental disorder – not otherwise specified (PDD-NOS) is defined by a later age of onset or by severe and pervasive impairment in one or two of the three core areas (APA, 2004). The causes of these disorders are varied and in many cases the specific etiologic agents have yet to be identified.

Family Studies

Epidemiological twin studies have shown a concordance rate of 36–96% for monozygotic and 0–30% for dizygotic AD twin pairs leading to an estimated heritability of >90% (Bailey et al., 1995; Folstein & Rutter, 1977; Ritvo et al., 1985; Steffenburg et al., 1989). There are no twin studies for AS and PDD-NOS; however, studies of families suggest that at least in some cases both AS and PDD-NOS can arise from similar genetic causes that can give rise to AD.

Candidate Genes

An increased risk of AD has been reported in single gene disorders including tuberous sclerosis (due to mutations in *TSC1* or *TSC2*) (Fombonne, 2003; Harrison & Bolton, 1997), fragile X (or *FRAXA,* due to the expansion of a CGG repeat in the 5′ untranslated region of the *FMR1* gene) (Fombonne, 2003; Reddy, 2005), Smith–Lemli–Opitz (SLO) (an autosomal recessive disorder resulting from mutations in the gene for Δ7-dehydrocholesterol reductase) (Sikora, Pettit-Kekel, Penfield, Merkens, & Steiner, 2006; Tierney et al., 2001), and PTEN (Buxbaum et al., 2007). Currently, more than 20 single gene disorders have been shown to sometimes present with an autism spectrum disorder phenotype (Schaefer & Mendelsohn, 2008; Veenstra-VanderWeele & Cook, 2004).

Recently, additional single gene disorders that present with an autism phenotype have been identified. These include mutations in NLGN3 and NLGN4 as well as SHANK3 (Durand et al., 2007). These genes are involved in the development, formation, and stabilization of synapses and implicate synaptic dysfunction as causative in some forms of autism spectrum disorders. This is supported by evidence that disruption of NRXN1 (Bourgeron, 2007) as well as CNTNAP2 (Bakkaloglu et al., 2008) can also be associated with autism spectrum disorders.

Extensive association studies with candidate genes, chosen based on both positional and functional criteria, have been carried out. These studies seek to identify genetic variants that may increase risk for autism spectrum disorders, but are not causal in the usual sense. For recent reviews see Veenstra-VanderWeele and Cook (2004), Wassink, Brzustowicz, Bartlett, and Szatmari (2004), Frietag (2007), and Sykes and Lamb (2007). Candidate genes that have been suggested to modulate risk for autism spectrum disorders include *GRIK2, EN2, SLC6A4, SLC25A12, RELN, NRCAM, WNT2, HOXA1, GABRG3, ATP10C*, and *UBE3A*. More recent findings include *PITXI* (Philippi et al., 2007), *ASMT* (Melke et al., 2008), *ITGA4*, and *STK39* (Ramoz, Cai, Reichert, Silverman, & Buxbaum, 2008).

Autistic spectrum disorder occurs primarily in boys (4:1 male to female ratio) while Rett syndrome is an X-linked dominant disorder occurring almost exclusively in girls. Rett syndrome is characterized by normal prenatal and perinatal development followed by loss of social engagement, deceleration of head growth, replacement of purposeful hand skills with

stereotyped hand movements, and impairment in expressive and receptive language development and gait (APA, 2004). The majority of Rett syndrome cases, up to 95%, are caused by mutations that result in loss or reduced function in *MECP2* (methyl-CpG-binding protein 2) on Xq28 (Amir, Sutton, & Van den Veyver, 2005; Amir et al., 1999; Chahrour & Zoghbi, 2007).

Genomic Studies

There are multiple chromosomal regions that have been linked to autism (Veenstra-VanderWeele & Cook, 2004). As recently reviewed (Freitag, 2007), cytogenic abnormalities associated with autism include 15q11–13 duplications as well as maternal and paternal 15q11–13 deletions (also associated with Angelman syndrome and Prader–Willi syndrome) and other deletions and duplications, including at 2q37, 22q13, and 22q11. The phenotypes associated with these deletions and duplications are varied and can include syndromal presentations, as well as additional psychiatric phenotypes.

In addition to cytogenetic abnormalities detectable by conventional approaches, microarray-based approaches are now allowing for the identification of smaller chromosomal changes, often called copy number variations (CNVs). Several studies using genome-wide analysis identified a recurrent microdeletion of a 593 kb region on chromosome 16p11.2 in simplex and multiplex families with autism (Kumar et al., 2008; Marshall et al., 2008; Sebat et al., 2007; Weiss et al., 2008). These large deletions may account for as much as 0.5–1% of cases in certain cohorts. These sorts of studies have identified many new CNVs in autism, most of which require further validation and study.

Gene–Environmental Interactions

As reviewed by Freiteg (2007), autistic traits have also been associated with prenatal exposure to thalidomide, valproic acid, and congenital rubella, as well as with untreated PKU. These disorders, which can present with an autism phenotype, are exceedingly uncommon. A great deal of controversy has surrounded the mumps–measles–rubella (MMR) vaccination and mercury exposure; however, studies do not support an association between these agents and the development of autism spectrum disorders (Committee, 2004; Fombonne, 2008; Shevell & Fombonne, 2006).

Summary and Psychosocial Implications

Several candidate genes and copy number variations have been associated with autism; however, the specific genes remain unknown. Rett syndromeis the only disorder with an identified mutation.

Genetic screening for Rett syndrome is clearly indicated since over 95% of cases are due to *MECP2* mutations. However, as over 99% are sporadic, arising de novo in the parental germline, no information about

recurrence risk is likely to be forthcoming (Trappe et al., 2001). In other autism spectrum disorder cases, there is an increasing number of chromosomal abnormalities, CNVs, and single gene mutations that can be screened for and can result in an appreciable diagnostic yield (Schaefer & Mendelsohn, 2008). Metabolic syndromes can also be screened for (Schaefer & Mendelsohn, 2008). The advantage of identifying the causes of autism in any particular case involves not only estimates of recurrence risk (which can be very high if the cause is an inherited mutation), but also understanding of the etiology that gives important information regarding disease trajectory (e.g., in the case of MECP2 mutations) and associated conditions that may require monitoring (e.g., tumors in cases of autism caused by PTEN mutations). Current array-based approaches are now receiving federal approval for genetic testing and we are sure to see an increase in the types of genetic variants that can be clinically identified in autism spectrum disorders. As the phenotype associated with even some of the most compelling genetic variants can be quite variable (e.g., 22q11 deletion syndrome is also associated with schizophrenia), interpretation of results will be challenging and will need to consider the amount of risk conferred by the confirmed genes and CNVs.

FORECASTING

Promises of Genetic Advances

The current state of genomic science holds great potential for unlocking the genes conferring risk for neuropsychiatric disorders such as ADHD, OCD, schizophrenia, and autism. Once identified, these genes will lead to the development of tests determining the involved dysfunctional neural pathways as well as targeted treatments and possibly cures.

This information could lead to significant advances in diagnosing neuropsychiatric disorders that currently rely primarily on clinical symptoms. Identifying an individual at high risk of developing a disorder could theoretically provide great benefit if the emergence of the disorder could be prevented with pharmacological or psychosocial interventions. Utilizing genetic testing to determine treatment response and adverse effects could lead to a speedier recovery.

Ethical Considerations

Along with the optimism generated by the potential advances, there is also apprehension because very little is known about how this information will be handled by individuals, their families, or society as a whole. For example, information on increased risk for a neuropsychiatric disorder could be very helpful in directing resources with the goal of preventing the evolution of that disease. Individuals with the short allele of the serotonin transporter have been reported to be at greater risk of developing depression, following stressful life events (Caspi et al., 2003) as well as self-injurious behavior (Anguelova et al., 2003). However, we do

not have any data on how this information would be used to redirect resources. We also do not know what effect this information will have on the individual, their family, or the evolution of the disease. A pilot study that provided families of patients with 22q11 deletions with the risk of developing psychiatric disorders (e.g., risk for developing schizophrenia is 25–30%) found that the possibility of psychiatric illness resulted in greater anxiety (Hercher & Bruenner, 2008). Individuals identified as rapid CYPD26 metabolizers have also been reported to be at increased risk for cancer (Sobti, Sharma, Joshi, Jindal, & Janmeja, 2003) and we do not know the impact of this information on individuals that may be depressed. Furthermore ethical issues regarding individuals with false-positive testing results remain unexplored. For example, as reviewed by Corcoran and colleagues, there are not any foolproof clinical methods for screening individuals at risk for schizophrenia (Corcoran, Malaspina, & Hercher, 2005). Even subjects that may present with prodromal symptoms of schizophrenia along with risk alleles may turn out to be a false positive and could be at risk of receiving treatment.

Neuropsychiatric disorders also have a history of significant stigmatization and the genetic information holds risk for potential harm. Parents may treat children identified with the risk differently, children may view themselves in a pejorative way; as may society. One of the greatest risks of genetic advances is that stigma will not be eliminated, but rather transferred in a fortified dose to those individuals identified as genetic carriers, as is suggested by a desire for increased social distance from individuals who were depicted with schizophrenia or major depression in vignettes (Dietrich et al., 2006).

TRANSLATION

Genetic Counseling

As reviewed by Austin (Austin & Honer, 2007), genetic counseling can be extremely helpful in providing individuals and families with current information and supporting them in understanding the information and coping with the implications for that particular family. We anticipate that individuals tested for neuropsychiatric disorders may have the same response as subjects in the Alzheimer's REVEAL (Risk Evaluation and Education for Alzheimer's Disease) study where subjects tended to recall primarily whether they had the *APOe4* gene and not the numerical risk of incurring the disease (Couzin, 2008). Given that neuropsychiatric disorders are polygenic and multifactorial, counseling can be invaluable in helping families understand that the presence of a risk gene variant does not necessarily lead to the development of that particular disease. For example, although heritability of schizophrenia is very high, concordance in monozygotic twins is only 41–65% (Cardno & Gottesman, 2000) suggesting that there are factors other than genes that play a very large role in the actual development of the disorder.

With regard to testing, at this time counseling could be very helpful to families in understanding that there are not any valid tests for any

specific neuropsychiatric disorders. Counseling could be helpful to families in understanding the potential benefits from CYP testing that could be useful in choosing and monitoring medications. This information could be placed in the context of other factors that could impact medication response such as age, developmental stage, methods of drug administration, interaction with diet, as well as ethnic diversity (Rasmussen-Torvik & McAlpine, 2007).

There is little data on whether individuals want genetic information with regard to neuropsychiatric disorders, and genetic counseling could help families deal with this issue. Some self-selection will occur in that individuals who do not want to know, will not be tested, or will not follow through with finding results following testing, as is reported in the Alzheimer's REVEAL (Couzin, 2008).

Although as reviewed by Lyus (2007) genetic counseling has the potential to enhance patient care, physicians have not been referring patients and families with neuropsychiatric disorders. This may be in part due to the fact that until recently, aside from the understanding that these disorders were familial, there was limited additional information. However, this is rapidly changing, and genetic counseling can provide invaluable information and support to patients and families. Studies investigating issues dealing with the actual handling of genetic information and impact on decision making will be very important.

Genetic Testing

At this time there are no valid single gene tests that are specific for any neuropsychiatric disorder. Surveys of attitudes toward psychiatric genetic testing among patients and families have reported a strong interest in testing that could be used for diagnoses and treatment, and to a lesser degree, for family planning (DeLisi & Bertisch, 2006; Laegsgaard & Mors, 2008).

Once the gene variants are identified, valid tests will undoubtedly become an optional part of the clinical evaluation. However, as reviewed by Biesecker and Peay (2003) it is important to note that the interpretation of the presence or absence of susceptibility genes for psychiatric disorders will be more complicated than for Mendelian dominant or recessive disorders. This is due to the fact that each gene variant may raise the risk slightly (e.g., from 1 to 2%) and most people with the variant will never develop the disorder. It is also likely that testing will need to include numerous potential variants, all with various levels for risk and for protection, as well as diverse frequency in different populations (DeMille et al., 2002). These factors may lead to misinterpretation and misunderstanding of results. A survey regarding genetic testing that included psychiatrists indicates a strong support for testing and nearly uniform support for informed consent, confidentiality, pre-test counseling, and post-test counseling by individuals who have demonstrated competence in interpreting test results (Hoop, Roberts, Green Hammond, & Cox, 2008).

Unfortunately, genetic tests for specific neuropsychiatric disorders are already being marketed in spite of the lack of substantial evidence for the gene variants that are included (Couzin, 2008). The marketing of these tests is raising a great deal of controversy, not only because of the lack of substantial evidence for the gene variants included but also because there is virtually no data on how information about genes relating to mental illness will be handled.

Pharmacogenetic Testing

Pharmacogenetic testing in neuropsychiatry, primarily CYP2D6 and CYP2C19 testing using the AmpliChip, may be useful in treatment and is currently being implemented, at least in academic centers (Mrazek, 2006).

As summarized by de Leon and colleagues (2006), CYP2D6 is the liver enzyme involved in the metabolism of 25% of medications including many antidepressants and antipsychotics. 2D6 has over 50 genetic variations that can be expressed with four levels of activity (ultra-rapid, extensive, intermediate, and poor metabolizers) depending on the number of copies of the active gene. Poor metabolizers essentially have no CYP2D6 enzymes in their liver and these individuals may have difficulty in tolerating antidepressants or antipsychotics metabolized through this pathway. Therefore, it may be safer to use psychotropics not dependent on CYP2D6 (e.g., bupropion, mirtazapine, sertraline) in poor metabolizers. The high rates of neuropsychiatric comorbidity frequently necessitate treatment with multiple medications and it is important to consider that some psychotropics (e.g., fluoxetene, paroxetine, bupropion) are strong CYP2D6 inhibitors rendering a patient who is an extensive metabolizer into a poor metabolizer. It is important to note, however, that limitations exist especially for ultrametabolizers. It was thought that this group had three or more copies of the active gene; however, this appears to be the case in only 20% (Chou et al., 2003) while the other 80% are not yet identifiable with current genetic testing (Bergmann et al., 2001). Testing of children and adolescence poses an additional ethical dilemma given that consent is provided by the parents.

Privacy of Genetic Information

A new issue of confidentiality is raised by data derived from genome-wide association studies. When a person is genotyped for over 500,000 SNPs, the genotypic profile is essentially a genetic "finger print" of that individual. Unlike rare disorders affecting only a small number of individuals, ADHD is a relatively common disorder and the risk of being identified only from the genetic data is theoretically very small.

The Genetic Information Nondiscrimination Act (GINA) aiming at protecting individuals from discrimination (e.g., from employers, insurers) based on genetic data has recently been passed into law (H.R.493). Essentially, the law prohibits health insurers from using genetic information in determining eligibility or setting premiums. It also forbids employers from using genetic information for decisions regarding hiring,

firing, job assignments, or promotions. The law prohibits health insurers and employers from requesting or requiring that individuals take a genetic test. However, the law does not address discrimination for life insurance and long-term disability insurance.

Privacy of information regarding genetic information within families is another issue that needs investigation. It is generally agreed that adults should have access to their own information, if this is what they choose, and parents should have access to their children's information. In a survey of mental health professionals, the majority of participants felt that adolescents, but not children under 12, should also have access to their own information (Mrazek et al., 2007). How this information would be provided to adolescents or younger children remains unexplored.

CONCLUSION

At this time, although we have not identified the genes causing ADHD, OCD, schizophrenia, and autism there is strong support for several candidate genes and CNVs conferring a small amount of attributable risk. The collaborative study groups currently recruiting larger cohorts that will be genotyped with higher-density chips that also allow the identification of copy number variations hold great promise. While past studies have relied primarily on clinical phenotypes, studies that include brain morphology and function are considered important in identifying genes with greater effect. Studies in children are also considered important in that these neuropsychiatric disorders with childhood onset may result from greater genetic liability.

The discovery of these genes is expected to bring about an increased understanding of these disorders as well as potential diagnostic tests and improved treatments. However, the effect of this information on the individual and the family is not yet known. The potential for harmful effects is recognized and plans to minimize these need further exploration.

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17

Genomic Risk Information for Common Health Conditions: Maximizing Kinship-Based Health Promotion

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The completion of the sequence of the human genome is rapidly increasing knowledge about the role of genetics in common health conditions. Scientific experts predict that the products that derive from this knowledge will lead to far-reaching advancements in public health and medicine in the decades to come (Lango & Weedon, 2007). Family health history and new genetic susceptibility tests, henceforward referred to as genetic risk assessments, may hold promise particularly for primary prevention of common health conditions (Collins, Meiser, Gaff, St. John, & Halliday, 2005). These "tools" have the potential advantage over other risk assessments of considering the complex gene–environment and gene–gene interactions that underlie disease risk. Moreover, they augur a future in which increasingly individualized risk information will be available.

Genetic risk assessments might be integrated with a diverse array of health promotion and disease prevention interventions. For example, family health history assessment provides a tool for health-care providers to evaluate clustering of risk factors and health conditions within families and enable them to customize prevention recommendations such as more frequent screening regimens. This customization in turn might

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increase the salience of providers' recommendations to individuals and their families.

Genetic susceptibility testing takes the potential for customized health assessment a level deeper. Genetic testing applications provide insights into the common genetic variability that increases risk for common diseases. New advances in the technology along with decreasing costs are paving the way for new tests that include hundreds of gene variants shown to, alone or in combination, increase risk for many common health conditions. While these tests enable individualized risk assessments, the gene variants and health conditions are so common that results also have implications for other family members. Eventually, this information may enable individualized behavioral recommendations that optimize primary prevention efforts.

In step with advances in genetic risk assessment are developments in basic science (e.g., neuroscience) and social ecological models of disease development. Taken together, these advances suggest that common disease results from a complex interplay of biological, cognitive, interpersonal, and social and physical environmental influences. Social influences have been widely considered in the field of adolescent psychology. For example, parents have been shown consistently to serve as important role models via processes that evolve and change throughout the course of child development (McHale, Dariotis, & Kauh, 2003). Children have other relationships such as with grandparents, friends, teachers, and community leaders that too can provide models of health behaviors (Kerr, Stattin, Biesecker, & Ferrer-Wieder, 2003; Roberto, Bolbin-MacNab, & Finney, 2008; Yaussi, 2005). Thus, the network of ties that impacts children's health behaviors can be quite broad and can be characterized as nested contexts comprising sets of interpersonal relationships such as that depicted in Figure 1 (Koehly & Loscalzo, 2009). Indeed, it has been widely held (Green, Richard, & Potvin, 1996; Richard, Potvin, Kishchuk, Prlic, & Green, 1996) that interventions that influence multiple contexts or levels of relationships could have the most far-reaching public health implications.

Genetics-informed risk assessment has implications at multiple interpersonal levels not only for the child but also for a broader social network. Of particular import is the kinship network, that is, the relationships among individuals who are related by blood, adoption, or marriage but who do not necessarily live together (Broderick, 1993). These social systems are characterized by a nexus of long-term relationships that often is the most proximal of social–environmental influences. Accordingly, available evidence suggests that up to 40% of individuals cite kin as their closest relationships (Hoyt & Babchuk, 1983; Shulman, 1975). Additionally, demographic trends over the past two decades – high rates of divorce, remarriage, single-sex parenting, and same-sex parenting – and increasing geographic mobility are broadening and increasing the heterogeneity of kinship networks (Schor, 2003). Yet, common to these networks are the patterns of shared meaning and transactional relationships of information-sharing, affection, support, power, coercion, conformity, and expectation (Loscalzo, 1998). Thus, kin often share ideas or hypotheses

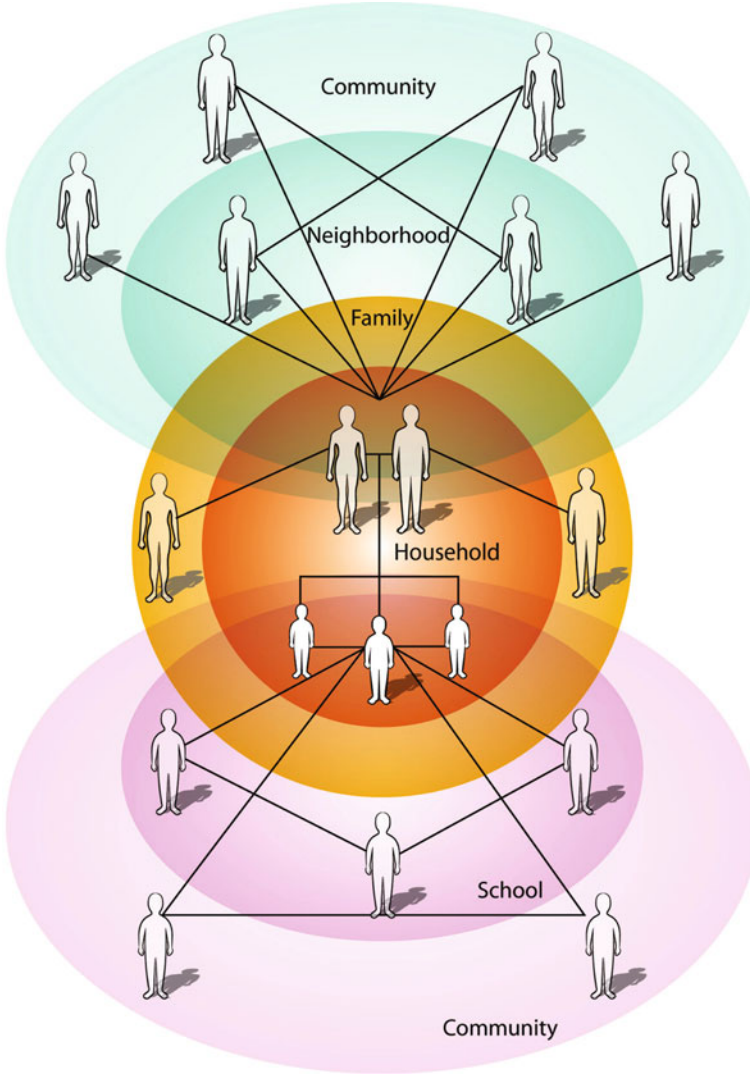

Figure 1. Nested social contexts surrounding children and their families. Adapted from Koehly and Loscalzo (2009).

about how the world operates and how members should cope with situations.

One posited benefit of genetic risk assessment (and the personalization it provides) is that it might, in combination with other intervention approaches, be used to encourage adoption of healthy lifestyles. These assertions have been conceptualized predominantly in terms of benefit to the individual. However, several conceptual models support that provision of genetic risk information and assessment might have benefit for broader kinship networks. Inclusion of kinship networks enables expansion of intervention reach from the individual to the broader relational context

that surrounds both children and their caregivers. Although social–ecological models have been emphasized in the social and behavioral sciences (Glass & McAtee, 2006; Green et al., 1996; Office of Behavioral and Social Science Research, 2001), implementation of an ecological approach to health promotion through relational contexts has lagged behind (Luke, 2005). Theories of interpersonal behavior (Kelley et al., 1983; Lyons, Mickelson, Sullivan, & Coyne, 1998; Rusbult & Van Lange, 2003), for example, consider how genetic risk information provided to one or more members could influence the behavior of the broader kinship network. These theories suggest that capitalizing on natural synergies within kinship networks might add value to current individual-based health promotion interventions. The Family Systems Genetic Illness model (FSGI; Rolland & Williams, 2005) also suggests a kinship-centered approach that considers the timing of disease onset (e.g., childhood/adolescent, early/mid adulthood, later life) and options for prevention (e.g., increased screening, health habits). In this model, the timing of disease onset and prevention options are posited to influence processes of information dissemination, support, and decision-making within the kinship network. The FSGI considers the course of risk as an ongoing process, where kin have different needs based on their placement in the timing of disease onset or risk; these systems change and evolve through each of the recognized phases and may differ depending on the life-stage of members within the kinship network.

However, these conceptually derived assertions about genetic risk and its influences on kinship networks have relatively little empiric support. Thus, it becomes important *now* to begin to consider whether and how emerging genetics-informed risk assessment tools might be applied to promote health within kinship networks and whether they add value above existing individual-based and family-based health promotion efforts. To this end, this chapter has been organized around three specific objectives: (1) to briefly characterize genetics-informed risk assessment "tools" currently or soon to be available for common health conditions; (2) to discuss evidence to support how these tools might improve kinship-based health promotion and prevention efforts; and (3) to make recommendations for future research directions.

GENETIC RISK INFORMATION: TOOLS OF TODAY AND TOMORROW

Family Health History

Family health history assessment, referred to henceforth as FHA, is currently the most widely accessible method for conveying genetic information about risk for common health conditions to individuals and families (Scheuner, Wang, Raffel, Larabell, & Rotter, 1997). A strong family history of a health condition, that is, having a first- or second-degree relative with early onset of said health condition or multiple first-degree

relatives with the condition, has been shown consistently to be associated with increased risk of heart disease, diabetes, and some cancers (Scheuner et al., 1997; Yoon, Scheuner, & Khoury, 2003). Compared to other risk assessments, FHA has the advantage of reflecting the joint contributions of inherited genetic susceptibility, shared environment, and lifestyle behaviors.

National surveys suggest that the majority of Americans (96%) view FHA as very important to their personal health (Yoon et al., 2004). However, far fewer, only 30%, report having collected information about their own family history. Moreover, surveys of primary care providers suggest that although they too regard FHA as important to their clinical care, they may not be fully receptive to incorporating suggested innovations into their clinical family history assessments (Jenkins, Woolford, Stevens, Kahn, & McBride, 2008).

In recent years, the importance of FHA for common diseases has been emphasized through public health campaigns such as the Surgeon General's Family History Initiative with the "My Family Health Portrait" (Guttmacher, Collins, & Carmona, 2004) and the Centers for Disease Control's (CDC) Family Healthware. The "My Family Health Portrait" has been promoted to the public via an annual public service campaign targeting Thanksgiving as an optimal time to collect family health history using the tool (Guttmacher et al., 2004). The "My Family Health Portrait" is currently available to the public, whereas CDC's Family Healthware is currently only available for research purposes.[1]

Each of these tools is web-based and each poses questions to the user about their own diagnoses of six common health conditions (e.g., type 2 diabetes, coronary artery disease, stroke, colorectal cancer, breast cancer, and ovarian cancer) as well as diagnoses of these conditions in their first- and second-degree relatives. The CDC's Family Healthware then generates risk feedback based on an algorithm of risk (Scheuner et al., 1997) and also provides screening and lifestyle recommendations based on the user's current screening patterns, lifestyle habits, and risk feedback. My Family Health Portrait allows the user to customize their FHA to risk factors and health conditions other than the six focal diseases. The ability to customize "My Family Health Portrait" allows individuals and health-care providers to characterize potential underlying mechanisms of risk through the clustering of risk factors and disease patterns within the family. For example, diabetes and heart disease tend to cluster within families, as do associated risk factors such as obesity and hypertension, representing the multifactorial etiology of common, chronic health conditions; a family health history indicating strong risk of diabetes would point to more frequent screening for hypertension, cholesterol, and blood glucose, beginning at an earlier age, in addition to increasing physical activity and, possibly, decreasing caloric intake (American Diabetes Association, 2008).

Although FHA has numerous advantages for estimating risk of common health conditions, there also are limits to its precision. For example,

[1]See http://familyhistory.hhs.gov

all children within a nuclear family have a similar genetic risk of disease based on a FHA, in that they share the same family history, yet they are each genetically different (Wray, Goddard, & Visscer, 2008). Information regarding age of diagnosis and death of blood relatives may be unavailable, and family members may be inaccurate in the information they have or recall (Qureshi et al., 2007). Additionally, family history of health conditions evolves and changes over time such that those at younger ages have less information about familial risk. Moreover, a sizable minority of the population is adopted and thus does not have ready access to their family health history.[2]

Genetic Susceptibility Testing for Common Health Conditions

Advances in technological infrastructure, the development of new analytical methods, and, most recently, the advent of new genotyping technologies are yielding voluminous amounts of genetic information related to common health conditions. Over the last 5 years, new genetic technologies have advanced at a pace analogous to that achieved by the microprocessor industry over the course of several decades. The number of single nucleotide polymorphisms (SNPs) that can be scored reliably in a single experiment continues to climb, whilst the price per genotype has declined by several orders of magnitude.

This combination of power and economy has led to a flood of genome-wide association studies.[3] These case–control studies have large enough sample sizes with adequate statistical power to identify associations among genomic factors (i.e., gene–gene and gene–environment interactions) and common health conditions. Indeed, the base of evidence to support the association of a number of genetic polymorphisms with increased risk for common health conditions is growing steadily and markedly. For example, several genetic variants have been identified as risk factors for type 2 diabetes (Saxena et al., 2007; Scott et al., 2007; Sladek et al., 2007; The Wellcome Trust Case Control Consortium, 2007; Zeggini et al., 2008) and these genetic variants may have combined effects that substantially increase an individual's risk for the disease. Additionally, genetic markers such as *FTO* (Dina et al., 2007) and *MC4R* (Loos et al., 2008) have been linked to biological mechanisms associated with obesity, such as resting metabolism and eating in the absence of hunger (Fisher et al., 2007; Kral & Faith, 2007; Wardle, Llewellyn, Sanderson, & Plomin, 2008).

The high-density single nucleotide polymorphism (SNP) arrays used to discover disease gene associations in populations also can be used to genotype individuals. Genetic susceptibility testing and newly emerging "multiplex" testing are expected to proliferate and be affordable in the coming decade. Most of the genetic variants associated with common conditions confer a small increased risk of disease. Thus, testing for these

[2]See http://www.childwelfare.gov

[3]See http://www.genome.gov/26525384

variants individually will likely not be informative. However, characterizing risk by including a panel of risk variants may generate a more accurate representation of an individual's risk (Janssens et al., 2006; Wray et al., 2008), and adding shared environment and other behavioral risk factors to genetic assessments can further increase their accuracy (Yang, Khoury, Botto, Friedman, & Flanders, 2003). Early renditions of these "multiplex" genetic susceptibility tests are already available providing "genomic profiling" or the characterization of an individual's constellation of genetic variants for a given health condition or set of conditions. These profiles and their associated risks are evolving as more information regarding contributing polymorphisms, gene–gene interactions, and gene–environment interactions come to the fore. However, as yet, these tests have not been evaluated with regard to potential benefits for motivating risk reduction. The great promise of genetic susceptibility testing is that it could be offered to the young and healthy, offering individualized risk assessment and the potential to move us toward true primary prevention of common health conditions.

Currently, there are over 1,500 genetic tests (over 1,200 available clinically, almost 300 available for research only) with the majority aimed at diagnosing or screening for rare health conditions.[4] Very few tests for common health conditions are yet available and none that have been deemed clinically valid or useful are available. Despite this, several companies have begun to offer whole genome scans that consumers can purchase from the web. One of note is "23andMe," which offers consumers information about their risk for common health conditions, along with other information about behavioral traits (e.g., sleep patterns), and the contribution of maternal and paternal DNA to these traits, as well as information about ancestry. 23andMe uses an "odds calculator" to combine genetic information, age, and ethnicity to evaluate risk for common health conditions based on the genetic profile. A second, "Navigenics Health Compass" also is being offered over the web directly to consumers. Navigenics provides a whole genome scan that includes over a million genetic markers of risk (SNPs and other genetic variation). For both of these tests, individuals are required to provide a saliva sample and pay $399–$2,500 as well as ongoing subscriber fees that enable them to receive updates on recent discoveries. The availability of these new technologies and the anticipation that the costs of these techniques will decrease precipitously suggest that more such commercial enterprises will arise in the future.

Opportunities and Challenges Raised by Genetic Risk Assessments

Genomic risk assessment may offer powerful tools to guide development of highly individualized primary prevention interventions to promote healthful lifestyles and prevent common health conditions. These

[4]See http://www.genetests.org

assessments could hold particular promise for primary prevention interventions targeted at young families.

Primary prevention is best achieved when interventions are targeted at the young and healthy and of greatest benefit in childhood before health habits are entrenched (Kemper, Koppes, de Vente, van Lenthe, & van Mechelen, 2002). Genetic risk assessments, in particular, genetic susceptibility testing could give kinship networks greater knowledge about their propensities to common health conditions before they experience even the earliest risk factors (e.g., elevated blood pressure, blood glucose, or lipids). The ubiquity and early onset of tobacco use and obesity provide excellent examples where FHA or genetic susceptibility feedback provided to kinship networks might increase the salience of taking action early and sustaining actions taken to reduce long-term risk for children. This information too could be used to address parents' misconceptions that children will avoid smoking due to their disapproval of parents' smoking or that children will "grow out" of baby fat.

Use of genetic risk information to engage kinship networks in healthier lifestyles also could increase the durability of intervention benefits. Although health promotion interventions generally show short-term changes in health habits, maintaining these changes in the long term is exceedingly difficult (Ory, Jordan, & Bazzarre, 2002). Most individuals who succeed in making behavior changes have high relapse rates in the year following participation in intervention. One possible advantage of kinship-focused genetic risk assessment interventions is that support for behavior change could be incorporated into the ongoing social environment. Thus, if genetic risk information could be integrated within family identity and evaluated as a common problem, one might expect that long-term maintenance of the health behavior changes could remain salient. These and other related research questions are yet to be considered.

Genetic risk assessment tools raise challenges as well. For example, the psychological impacts of finding out that one is at slightly increased risk for health conditions are largely unknown, and the potential negative impacts this information might have on children and young families raises considerable concern. Individuals who receive genetic risk assessments may be unnecessarily distressed or mistakenly reassured about their risk of developing a chronic condition (Prainsack et al., 2008). Additionally, it has been suggested that genetic risk assessments may negatively influence parenting practices or interrupt identity formation in children (Fanos, 1997). Yet, there is little empirical support for these concerns.

Moreover, communication dynamics amongst kinship networks may lead to misunderstandings or miscommunication of test results, in ways that negatively influence health outcomes (Ciarleglio, Bennett, Williamson, Mandell, & Marks, 2003; Prainsack et al., 2008). Most of the genetic variants are associated with only small increases in risk for common health conditions and there is little understanding of the biological mechanisms through which these genes influence risk (The Wellcome Trust Case Control Consortium, 2007). Further, pleiotropic effects, where a single gene may be associated with multiple disease outcomes, may further challenge understanding of genetic risk information, particularly in the

case of antagonistic pleiotropy, where the expression of the gene is beneficial or protective for one health condition and detrimental for another. Given the scientific community's limited understanding of the genomic etiology of common health conditions, it is not surprising that educating the public as to the meaning of genomic risk information will be challenging. However, public confusion already has been documented in other health contexts, for example, with respect to dietary recommendations (Boyle, Boffetta, & Autier, 2008). Ideally, new knowledge about individual genetic differences in response to environmental exposures might help to explain the apparent contradictions of health promotion research findings based on heterogeneous samples.

The use of genetic tools to assess risk for common health conditions also will require that primary care health professionals learn about genetics so that they use this information in their clinical practice (Guttmacher, Jenkins, & Uhlmann, 2001). Health-care providers will not only need the knowledge to interpret genetic risk information and give its meaning to their patients, but also play a key role in encouraging their patients to obtain accurate FHA information from kin, share their own health information within their kinship network, and encourage the kinship network to engage in health-promoting behaviors. While insurance costs and employment discrimination have often been named as barriers to obtaining genetic-based risk assessments or disclosure of genetic risk information, the recent passage of the US Genetic Information Nondiscrimination Act (GINA) is anticipated to alleviate associated fears.[5]

The opportunities and challenges for translating genetic risk assessment to kinship-based health promotion interventions and related clinical practice are considerable. Much research is needed to understand how such information can be optimally disseminated within the family and whether or not it will affect the adoption of healthy lifestyles and the seeking of medical interventions (i.e., screening and treatment) that can lead to the overall reduction in disease burden (Khoury, Valdez, & Albright, 2008).

GENETIC RISK INFORMATION AS PART OF KINSHIP-BASED HEALTH PROMOTION EFFORTS

The increasing availability of genetic risk information raises an obvious question about how this emerging knowledge might be used to improve the health of kinship networks. Despite the widely acknowledged influence of kinship networks on a wide range of adult and child health behaviors (Delva, Johnston, & O'Malley, 2007), family-based approaches generally have been under-utilized as a health promotion intervention strategy (Bauman et al., 2001; Kitzmann & Beech, 2006). Thus it is not surprising that informal review of the literature via Pubmed based on a combination of key words (e.g., family-based, intervention, behavior

[5]The Genetic Information Nondiscrimination Act of the National Human Genome Research Institute: http://www.genome.gov/24519851

change, family history, genetics, health promotion) showed little research that considers the value of providing genetic risk information as part of health promotion interventions. There were no studies that examined the role of multiplex genetic susceptibility testing and very few that have considered multiple behavioral risk factors simultaneously. Indeed, most of the studies considered familial risk only with regard to sample selection. For example, most studies used genetic risk, primarily FHA, to identify high-risk families within a single disease context and then focused health promotion efforts on an individual family member. Where possible we highlight examples of studies that have included genetic risk assessment (1) to consider naturally occurring risk synergies within kinship networks and (2) in ways that could have an affect on the potency of health promotion intervention efforts.

Considering Naturally Occurring Risk Synergies

There are numerous reasons to suggest that genomic information might improve upon health promotion interventions. Interdependence theory and the other conceptual models described earlier suggest ways in which interventions might take advantage of the kinship networks or subgroups within these networks to promote health and, in turn, how genetics-informed risk information might add to the potency of these interventions.

That common health conditions "run in" kinship networks is well established. Evidence shows the substantial heritability (30–80%) of common health conditions such as type 2 diabetes, coronary artery disease, hypertension, and several cancers (Lango & Weedon, 2007). Most general surveys suggest that the public appreciates that family history influences risk of health conditions. However, the public's understanding of inheritance patterns is fraught with misconception (Walter, Emery, Braithwaite, & Marteau, 2005).

Additionally, shared environmental factors also are well-known contributors to risk for common health conditions within families. A large and growing body of research shows that risky lifestyle habits such as cigarette smoking, poor diet, and physical inactivity aggregate within kinship networks. Prospective family cohort studies conducted around the world consistently show that alcohol consumption, body mass index, and dietary fat intake of parents and their young children are highly correlated and remain correlated prospectively into young adulthood (Burke, Beilin, & Dunbar, 2001; Norton, Froelicher, Waters, & Carrieri-Kohlman, 2003; Ohrig, Geib, Haas, & Schwandt, 2001). Household composition, including the number and density of household members, also has been shown to influence health behaviors. For example, the number and gender of children in the household, as well as the number of parents, has been associated with children's sedentary behaviors, as indicated by television-viewing habits (Bagley, Salmon, & Crawford, 2006).

Health promotion interventions have begun to consider the simultaneous and interdependent influences of these multiple environmental factors (Orleans, 2004) and the few conducted have been shown to be

effective (Elmer et al., 2006). However, they have targeted only the individual. Yet to be considered is whether the challenges of interventions that address multiple environmental risk factors might be lessened by involvement of kinship networks and inclusion of genetic risk information. Interdependence theory suggests that this might work via "communal coping," that is, coping need not only be an individual-level cognitive phenomenon but can occur conjointly within kinship networks when the network is faced with a shared threat (Afifi, Hutchinson, & Krouse, 2006; Lewis et al., 2006; Lyons et al., 1998). When a shared health threat is perceived as a family-level problem, network members may take a cooperative problem-solving approach. In so doing, they may engage in reciprocal exchange of support (Antonucci & Jackson, 1990; Emmons et al., 2005; Koehly, Peters, Kuhn et al., 2008) or use pooled or shared support resources (Koehly et al., 2008; Lyons et al., 1998). Support resources may be characterized by information exchange, emotional support, or tangible assistance (House, Umberson, & Landis, 1988), as well as encouragement processes or co-engagement in health-promoting behaviors. Genetic risk information might be particularly effective in prompting kin to view health habits and related outcomes as a shared problem requiring joint action. For example, awareness that a relative has genetic-based risk factors might influence other family members' cognitive and emotional interpretations of what this information means for the broader kinship network. These interpretations could motivate cooperative problem solving including voluntary changes on behalf of other family members who are regarded to be at genetic risk. In turn, this cooperative problem solving might mobilize the kinship network toward lifestyle change and general health promotion (Lyons et al., 1998).

What we currently know about these communal coping mechanisms has been based on dyadic interdependence: spousal relationships (Lewis et al., 2006) or parent–child relationships (Haire-Joshu et al., 2009). This research has established that parent and child health behaviors are reciprocally influenced (Rimal, 2003). Parents, and mothers in particular, are important models of health habits (Bricker et al., 2006). Parents, in turn, recognize the importance of modeling healthy habits for their children and desire to preserve children's well-being; this reciprocity can be a powerful lever that can and has been used to encourage families to engage in healthy lifestyles (Bauman et al., 2001).

Information processing models suggest that familial or personal genetic risk information also could be regarded as highly salient and of significant personal importance in ways that could benefit and broaden health promotion efforts beyond the individual (Kahlor, Dunwoody, Griffin, Neuwirth, & Giese, 2003). Genetic risk information more so than *generic* information might capture the attention of individuals and in turn their kinship networks to consider personal and family risk conjointly (Johnson, Case, & Andrews, 2005). This perceived salience may engage individuals and kinship networks in making greater efforts to understand the impact of risk on health which, in turn, prompt increased communication regarding shared risk within the network. There is then a greater likelihood of shared appraisals of risk, thus, motivating cooperative

approaches to encourage appropriate screening behaviors and adoption of health-promoting behaviors.

Family history-based interventions. One of the few examples of a genetic risk informed health promotion intervention was the "Health Family Tree" study (Johnson et al., 2005; Williams et al., 2001, 1988) initiated over 20 years ago and based in Utah and Texas. This intervention engaged high school students in a project to construct a family health history that included disease status of first- and second-degree relatives. The intervention had dual objectives: (1) to educate students about the disease risk in their family and (2) to identify families at high risk for specific health conditions that were appropriate for more intensive family-based interventions. The first phase of the intervention took place as part of a mandatory health education class in which students were instructed to take home a fold-out family tree schematic and to complete it with the assistance of family members. The health education teachers leading these classes attended trainings in which they were provided with lesson plans on the importance of family history. Consistent with the new web-based FHA approaches, a computer-generated report was mailed directly to each family including feedback and advice for each disease and risk factor included in the report. In the second phase, families identified to be at high risk were offered home visits by public health nurses who could make appropriate referrals to health-care providers and assist with behavior change skills. Multiple family members, with shared risk of disease, were invited to participate, and involvement was reported to be "high." The high-risk families reported increased motivation to make long-term behavior changes. At the 10-year follow-up, Johnson and colleagues also reported that rates of health screenings were higher and that health behaviors improved among families that received the nurse-led family-based intervention (Johnson et al., 2005).

Other interventions have targeted adult siblings (Becker et al., 2005) and adult or teenage children (Salminen, Vahlberg, Ojanlatva, & Kivela, 2005; Walker, Heller, Redman, O'Connell, & Boulton, 1992; Wing, Venditti, Jakicic, Polley, & Lang, 1998) of those who have experienced myocardial infarction, those at high risk for cardiovascular events or adult onset diabetes. These studies have typically involved nurse practitioners as interventionists who work with the family members to raise their awareness of the familial nature of these health conditions and to encourage risk reduction. Like the Health Family Tree study these intervention approaches were relatively intensive, taking place in the home or as part of serialized group meetings. Despite their intensity they had variable success. Adult siblings who received the intervention were found to have greater rates of controlled blood pressure and lipid levels than the comparison group (Becker et al., 2005), whereas teenagers (Walker et al., 1992) who received intervention were more likely to report reductions in dietary fat intake relative to the comparison group, but their blood cholesterol levels actually increased during the intervention follow-up. In the other trial with teenagers, there was no benefit shown from the intervention (Salminen et al., 2005). A lifestyle intervention with adult children of parents with diabetes showed short-term improvements in weight loss, eating,

exercise and fitness (Becker et al., 2005). However, these improvements were not sustained at 24 months follow-up. It is noteworthy that none of these interventions have attempted to capitalize on the affective and influential nature of social relationships within the kinship networks to encourage risk reduction behaviors.

Genetic susceptibility testing interventions. With regard to genetic testing, the majority of research to date has evaluated kinship networks' responses to genetic risk feedback for Mendelian-inherited conditions such as familial cancers and Huntington's disease (Barsevich et al., 2008; Klitzman, Thorne, Williamson, Chung, & Marder, 2007). These interventions have aimed to assist families in making appropriate screening and medical management decisions rather than general health promotion as an outcome. Results consistently have shown the interpersonal and interdependent nature of responses to genetics-informed risk feedback. Multiple studies have shown that adults who seek such testing do so because they believe the risk information may have importance for their children (Lerman, Croyle, Tercyak, & Hamann, 2002). Although barriers to disclosure of genetic risk information within kinship networks have been identified (Claes et al., 2003; MacDonald et al., 2007; Wilson, Forrest, & van Teijlingent, 2004), study participants have generally expressed positive views about informing family members about inherited cancer risk (Hallowell et al., 2003; Hughes et al., 2002; Kenen, Arden-Jones, & Eeles, 2004; Peterson et al., 2003; Wilson et al., 2004). Participation in genetic education and testing largely has been effective as behavior change interventions, resulting in focused early detection screening and medical management (Botkin et al., 2003; Claes, Evers-Kiebooms, & Decruyenaere, 2005; Collins et al., 2005; Hadley et al., 2004; Halbert et al., 2004; Lerman et al., 2000; Scheur, Kauff, & Robson, 2002; Watson et al., 2005). Moreover, talking about family-level risk with family members and in turn, receiving encouragement from family members to screen has been shown to increase adherence to colorectal cancer screening in Lynch syndrome families (Ersig, Williams, Hadley, & Koehly, 2009).

It is important to note that studies of familial cancer syndromes have involved self-selected samples of predominantly highly educated white females, potentially limiting generalizability to more diverse populations. Further, it is unclear whether the findings from studies of Mendelian-inherited conditions will generalize to the case of new genetic susceptibility testing for common health conditions where test results will be much less predictive, more probabilistic, and reflect risk on multiple health conditions simultaneously. Current recommendations of several national advisory groups (Bookman et al., 2006) that genetic test results related to common diseases are not yet appropriate for return to individuals, even participants in research studies, has limited advancement of research to understand the potential use of this information in the general population (McBride & Brody, 2007).

As mentioned earlier, there is almost no research exploring how the added personalization of genetic susceptibility testing might compare to FHA in the context of conveying risk for common health conditions. The closest evidence that begins to bring light to this issue comes from the

REVEAL study that was conducted with individuals from families affected by the most common form of Alzheimer's disease, that is, late onset. This study (LaRusse et al., 2005) evaluated the effects of providing identical levels of risk to women. However, half were randomized to receive the risk feedback based on genetic susceptibility testing for *APOE4* and the other half received feedback based on FHA. Women reported a more positive impact of the genetic risk information than those who received FHA. Disclosure of *APOE* genetic test results among family members was more limited than that observed in the hereditary cancer literature (Patenaude et al., 2006); 64% shared results with their family members (Ashida, Koehly, Roberts, Chen, Hiraki, & Green, 2009). This may indicate important differences in how families communicate about disease risk when it is based on genes with low penetrance. Questions about how this type of personalization with respect to risk of other common health conditions might affect engagement, and in turn diffusion of information within a kinship network, have not yet been considered. Moreover, the effects of combining FHA and genetic susceptibility feedback that would have relevance to the broader kinship network while providing highly individualized risk information to individuals within the network also have not yet been considered.

Similarly, only one study has offered genetic susceptibility testing in the context of a family health event involving a common health behavior and common disease. Sanderson and colleagues report the results of this small pilot study in which smokers who were relatives of recently diagnosed lung cancer patients were offered genetic susceptibility testing related to lung cancer to evaluate the influence of such testing on uptake of smoking cessation services (Sanderson et al., 2008). Findings suggest that smokers who considered such testing were highly motivated to quit and so showed no differences by genetic test results on interest in free smoking cessation aides. Although multiple members of the kinship network were offered the testing, the feedback approach did not take advantage of any aspects of the social network or the smokers' relationship with the lung cancer patient.

FUTURE RESEARCH NEEDS

As the previous sections demonstrate, research to understand and take advantage of the potential of kinship-based health promotion efforts is underdeveloped. We predict that ongoing advances in genetics and genomics will put increasing pressure on health promotion efforts to move beyond the almost exclusive focus on the individual to consider the broader kinship relationships that influence health. However, the limited extent of general kinship-based health promotion research presents a daunting backdrop upon which to consider priorities for future research. Moreover, these efforts also will be challenged by considerations of public health translation that will require these interventions to be effective, economical, and amenable to broad dissemination.

To this end, we suggest that future research efforts be focused on three thematic areas: (1) to identify whether and how genetic risk information might be used to capitalize on kinship social structure to promote healthy lifestyles, (2) to develop intervention components and measures of the individual and interpersonal impact of the interventions, and (3) to develop statistical methods for considering how the characteristics of kinship networks influence the effectiveness of interventions.

The dearth of research in genetics, kinship networks, and health promotion raises questions about what should be the research priorities within these thematic categories. Campbell and colleagues (Campbell et al., 2000) suggest taking a systematic and phased approach that can be conducted linearly or simultaneously (see Figure 2). They suggest that within each thematic area, early research studies be identified to address "preclinical (theory)" issues, that is, to bring conceptual understanding to create testable hypotheses. For example, phase 1 research might apply information processing models (Kahlor et al., 2003) or similar conceptual models to suggest hypotheses about the unique challenges of disseminating genetic information within social networks, and specifically how these patterns may influence how and when children are told about risk and whether they will comprehend the importance of such information. This information in turn could be used in phase II studies, where family communication support interventions are created and evaluated for their feasibility and child-relevant intervention outcomes are developed and evaluated. This phase is then followed by large phase III trials which can be considered once enough phase I and II data demonstrate the safety and optimal interventions, and the evaluation on children and family outcomes

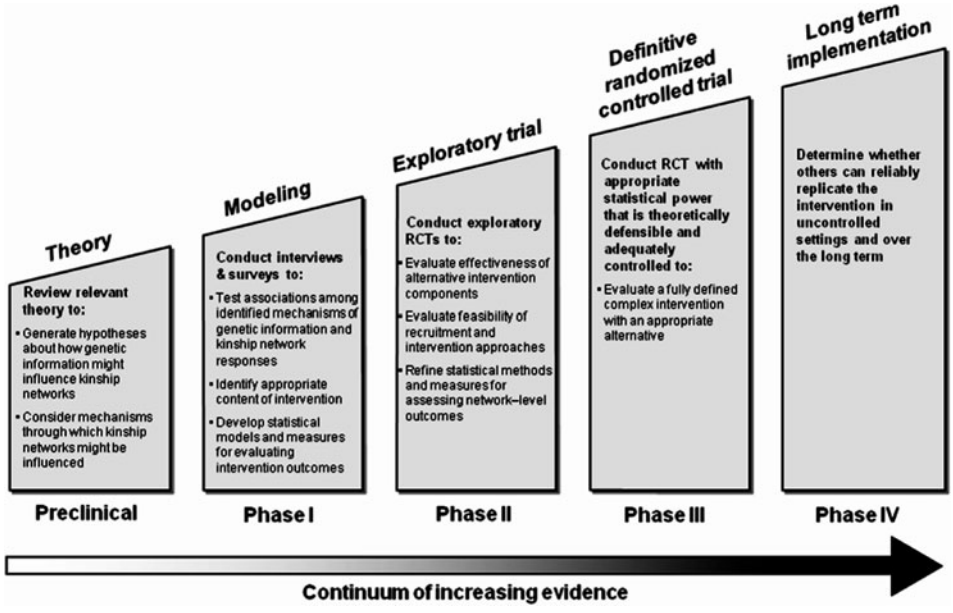

Figure 2. Adaptation of the Campbell et al. (2000) framework for multi-phased research.

can be rigorously evaluated. In the next sections, we suggest examples of research for each of the three thematic areas described above in keeping with the phased approach suggested by Campbell and colleagues.

Capitalizing on the Kinship Social Structure to Promote Health

Kinship-based health promotion interventions could target any one of several theory-based mechanisms such as interdependence theory, processes of communal coping, or information processing models. As yet, it is unclear whether information implying shared genetic risk for common health conditions, such as type 2 diabetes or heart disease, increase shared appraisals of risk and communal coping efforts to address this shared risk. Research characterizing patterns of information-sharing among the network, as well as shared appraisals and coping that result, will be instrumental in defining strategies that could be embedded in future health promotion interventions.

To this end, methodologies that provide an understanding of the family social structure and how that structure affects and is affected by genetic risk information will be particularly important (Patenaude, Guttmacher, & Collins, 2002). Tracking the flow of information regarding shared risk of disease is an important initial step in understanding whether and how common perceptions of a health threat are established (Koehly et al., 2003; Stoffel et al., 2008). It will be important for intervention development to address questions such as when and how is risk information shared within kinship networks, are all members equally receptive to the information, and what characteristics of the network and other contextual factors influence these patterns of communication?

Additionally, research to characterize the social influence structure within kinship networks is also needed. For example, are there particular nodes of influence, that is, individuals within the kinship network who might be optimal information disseminators. The hereditary cancer literature indicates that women tend to take on the role of "kin keepers" (Koehly et al., 2003), suggesting that female family members may be the best disseminators of family risk information, whereas parents tend to take on the role of information gatherers representing their role as "gate keepers" of health information between older and younger generations (Koehly et al., 2009). In these cases of familial cancer syndromes, the risk conferred on individuals who carry the mutation is high (50–80% increased risk). In the case of common health conditions, genetic variants will be associated with only slight increases in risk (10–30% increased risk). Thus, it is unclear whether the latter information will be viewed as less threatening and discussed more openly or not regarded as important enough to convey among kinship networks. In these cases, women may continue to take the role of family health historian or responsibility might become diffused due to the lower risk perception. Moreover, how the cultural context influences this process among kinship networks is largely unknown.

Also of great importance to future research is the consideration of how these communication patterns might influence health behaviors. In our work with Lynch syndrome families, we have identified a "family-encourager communication model"; that is, family members who encourage many family members to seek cancer screening and tend to screen themselves are the "family encouragers." In addition, those being encouraged also tend to engage in more appropriate screening behaviors. This model appears to be more effective than when encouragement is more diffused and family members encourage each other in a form of a "buddy system" (Koehly & Hadley, 2008). However, to our knowledge, there is no ongoing research to explore whether these kinship-based processes are taking place with respect to family history of common diseases or growing public awareness of the genetic underpinnings of common health conditions. Clearly, a good deal of preclinical and phase I research is called for to begin to explore these mechanisms.

Evaluation of Genetics-Informed Intervention Programs to Improve Health

Consistent with phase II, many questions are yet to be explored about how best to package strategies and combine elements deemed essential to the effectiveness of kinship-based health promotion efforts. Once strategies have been identified, the question remains of how to best achieve parsimony and create an effective intervention program. For example, once the characteristics of optimal disseminators have been elucidated, are these individuals willing to play this role and what support do they need to be most effective; what will the challenges be to recruitment and participation; and how should benefit be measured, at the level of the individual, interpersonally, or the broader network?

One of the unique challenges presented by genetic-informed interventions is variability in how sensitive genetic risk information is regarded by different target groups. For example, concerns have been raised about the age at which it is appropriate to provide individuals with genetic risk information (Duncan & Delatycki, 2006). Sensitivities among minority communities also have been questioned, given historical abuses of genetic information (Sterling, Henderson, & Corbie-Smith, 2006). How these issues are considered and addressed also provide considerable fodder for early phase research efforts. For example, health promotion objectives are best achieved among the young. Indeed, eating patterns, tobacco experimentation, and activity patterns are set in early childhood. However, concerns have been raised about offering genetic-based risk assessment to those under the legal age of consent (Valdez, Greenlund, Khoury, & Yoon, 2007). These concerns center around the unknown social and psychological effects of labeling children as "at risk," the impact this may have on identity formation, and the largely unknown potential for long-term influences related to insurance or other forms of discrimination (Malpas, 2008). The limited evidence available suggests that young adults and youth see advantages in genetic testing for both Mendelian-inherited

conditions (Bradbury et al., 2008) and common complex health conditions (Tercyak, Peshkin, Wine, & Walker, 2006). Only one study has explored the experiences of young adults who have undergone genetic testing (Duncan et al., 2008). Young adults who had undergone genetic testing for familial adenomatous polyposis (FAP) or Huntington's disease report a mix of positive and negative psychological experiences.

Yet, when asked, parents not only favored testing children but the majority also considered it appropriate to test young children. In one qualitative study, Segal and colleagues (2007) reported results of focus groups with multi-ethnic parents and found that the majority of white parents felt that testing should occur at birth, whereas Hispanic and African-American parents favored testing children aged 5 and older. A number of possible iatrogenic effects of conveying genetic risk information to parents also have been suggested. Parents who learn of genetic risk might become over-focused on children's behaviors in ways that do not promote health improvements. Indeed, family-focused interventions for obesity prevention have shown that when parents over-monitor their children's eating habits, they may undermine children's healthy eating choices (Arredondo et al., 2006).

Many other pressing questions relating to intervention implementation must be addressed. For example, it is also unclear what the optimal duration of kinship-based interventions should be, or how many members of the network need to be involved to maximize intervention effects; how do we measure intervention outcomes, and what individual-level indicators might be surrogates of broader network level improvements? Moreover, what are the possible network level outcomes of these interventions?

Development of Statistical Methods for Kinship Networks

One of the main barriers to implementing and evaluating kinship-based health promotion efforts is the considerable methodological challenges. Because influence processes are primarily relational, methods that measure and model the structure and function of these relationships are needed. Social network methods enable the social relationships that comprise kinship networks, including children, their parents, and extended families, to be considered statistically. In this way, for example, optimally located family members can be identified who might be recruited to serve as family health advisors or family encouragers. Additionally, social network methods include statistical tools that can be used to evaluate the effectiveness of kinship-based health promotion interventions by modeling, directly, changes in communication patterns, development of shared appraisals of risk, and cooperative strategies to modify risk.

Kinship networks represent a complex, interconnected system of relationships, requiring methods that can adequately measure and model this complexity. Social network methods represent one methodological approach that can account for the complex interdependencies among family members. Currently social network methods rely on two approaches: (1) complete network methods, which accommodate relational systems

that are bounded where all network members within these bounds provide information on their social interactions, or (2) ego-centered networks where the focus is on relationships that surround a set of unrelated individuals (Wasserman & Faust, 1994). The complete network approach would give truest insight into the network relations as it would include the unique perspectives of all network members concerning their relationships with all other group members. Unfortunately, there are several challenges to measuring complete kinship networks. First, as discussed earlier, the boundaries of modern kinship networks are not easily defined and each member may define these boundaries differently. Additionally, given the sampling methods that are commonly used in studies of families (e.g., cascade or snowball sampling) and the need to be compliant with human subjects' protections, we rarely can obtain relational measurements from all family members.

Thus, measurement and modeling approaches that can account for "unboundedness" of modern kinship networks and accommodate non-respondents need to be developed. One approach that warrants further research is a design in which a series of ego-centered networks is obtained from individuals who report lists of those who they think of as family, defining their kinship "neighborhood" (Pattison & Robins, 2002); then, the functional types of relationships that are provided by each family member are measured. These ego-centered networks can be aggregated to obtain an incomplete but multidimensional picture of the kinship network. There will be some missing relational information because not all members are providing their ego-centered networks, either due to non-referral, refusal to participate, or possible ineligibility. Social network analysis can then be used to depict these interconnected relational structures and network indices can be constructed. For example, centrality and prestige, structural characteristics of network members' importance or prominence in the group, could be used to identify "key informants," information gatherers," "family encouragers," and shared resources. These indices of relatedness, however, need to be adjusted to account for the number of respondents and missing information.

Statistical models for network data also can be used to test hypothesized changes in density, reciprocity, or cliquing within the network. The network *density* would indicate the rate of participation or communication within a network; *reciprocity* represents mutual exchange of a resource between two network members, such as between a parent and their child; and *cliquing*, or pockets of cohesion identified among subsets of network members, may provide insight into those subgroups of kinship network members who are engaged in encouraging adolescents' healthful behaviors. These exponential random graph models (ERGMs) have been developed for complete networks. ERGMs can be modified to adjust for the very common occurrence of having incomplete kinship networks data through the definition of "kinship neighborhoods" and the mathematical linkage between ERGMs for complete networks and ego-centered networks (Koehly, Goodreau, & Morris, 2004). Efforts are currently underway to evaluate the accuracy of these incomplete network models and provide recommendations regarding the minimal response rate necessary to

address network or relational questions of interest [available upon request from LK].

As described earlier, communal coping studies have largely been limited to dyadic relationships. The interdependent nature of the communal coping model requires tools that can quantitatively account for the connections among those coping together. One advantage of using a social network approach is that the unit of analysis can extend beyond the dyad to triadic or larger group structures that can account for relational ties between children, their parents, and other family members, the most proximal set of social influences on child behavior. From a theoretical perspective, it is likely that network processes involve different functional types of relational ties. Although social network methods can inform the structural characteristics that may underlie interdependence theories, such as communal coping, measuring appropriate functional relationships among network members needs further inquiry. For example, one of the key components of the communal coping model is the development of cooperative strategies. The measurement of cooperative problem solving is a function of the type of relationships measured as well as structural characteristics within the kinship network. The social support literature provides guidance on measuring several different functional domains, including information exchange, emotional support, and tangible assistance (Sarason, Levine, Basham, & Sarason, 1983). However, family-based health promotion efforts informed by genetic-based risk assessments may require new measurement tools. These tools could capture communications specific to genetic susceptibility or family health history of common health conditions, encouragement to screen or modify behavior, or co-engagement in health-promoting behaviors.

Clearly, moving from individual-based intervention approaches to interventions that focus on the kinship network requires new measures that capture the relational constructs unique to theories of interdependence and communal coping. Further, statistical models are needed that can evaluate how relationships change following intervention and the relational processes that may facilitate or inhibit the adoption of health promotion and disease prevention behaviors among family members. It is essential to continue efforts in developing more sophisticated methodological tools that can be used to measure and model the complexities of the kinship network and assess the effectiveness of intervention components.

CONCLUSIONS

Health promotion interventions have focused almost exclusively on the individual without due consideration of the social context within which risk communications and health behaviors occur (Glass & McAtee, 2006). Ironically, as we learn more about the genetics of common, chronic diseases, we also gain greater appreciation of the complex, but central, role of environmental influences. In this way, advancing knowledge about genetic contributions to risk for common health conditions will require health

promotion interventions to look beyond the individual to the broader social environment for ways to influence healthy lifestyles.

In this chapter we suggest that kinship networks are an important component of this web of social ties that could be targeted for intervention. It is well established that social, behavioral, and genetic risk factors cluster within these kinship systems. Attesting to this are data from the Framingham Heart Study showing that obesity clusters according to both biological and social ties and that change in weight status could be attributed to these shared relationships (Christakis & Fowler, 2007). The same social factors influenced rates of smoking cessation (Christakis & Fowler, 2008). Thus, it is clear that the web of social ties that connect individuals must become a more central consideration of health promotion efforts.

Interventions that capitalize on these resources and motivate cooperative problem solving among family members may be particularly effective. Research to consider how to integrate new genetic advances with kinship-based health promotion efforts to prevent common health conditions has tremendous potential public-health benefit that as yet has been largely unexplored. Multi-phase research is needed to capture the relational processes underlying kinship responses to genetic risk information. This research could culminate in a detailed map of the social environment within which network members interact and suggest innovative approaches to designing health promotion interventions. Using a social network approach could provide us with the framework to understand the social environment of different kinship networks and how these environments might be capitalized on using genetic risk information to increase health-promoting behaviors (Koehly & Shivy, 2000; Lyons et al., 1998).

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Part IV

Emerging Issues

18

Pediatric Pharmacogenomics

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Over the past several decades, one of the most fascinating achievements is the completion of the first draft of the human genome followed by subsequent creation of the map of human genetic variation. With these accomplishments in the human genetics field, scientists now have a better understanding on human diversity at the molecular level. It has long been known that the responses to many commonly used drugs vary greatly among patients. For example, when the same dose of the same drug is prescribed to a group of patients diagnosed with the same disease, some may respond to the treatment as expected, some may have no therapeutic response, whereas others may suffer clinically toxic or even fatal adverse effects. In general, the way a person responds to a medicine is largely genetically determined (Caraco, 2004).

'Pharmacogenetics' is a science that investigates the relationship between drug responses and inherited variations in genes. Since most drug responses are influenced not only by one single gene alone but also by many different genes across the human genome, the term 'pharmacogenomics' has been introduced – referring to the study of the entire spectrum of genes involved in drug response (Shastry, 2006). Although 'pharmacogenetics' considers one or at most a few genes of interest and 'pharmacogenomics' considers the entire human genome in drug responses these two terms tend to be used interchangeably, and a precise and consistent definition of each remains somewhat elusive. Today, 'pharmacogenetics' and 'pharmacogenomics' both represent studies on fundamental gene–drug response relationships. These studies provide the basis to better understand the mechanisms of inter-individual differences in drug response and explore potential ways of using genetic variations to improve health and the delivery of health-care services.

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Compared with adults, the pediatric population represents a unique pharmacogenetic challenge as children have additional complexity. Drug-metabolizing enzymes, transporters, and the targets which play important roles in drug responses may vary along developmental stages. Therefore, the interaction of genetic and developmental factors may contribute to the increased susceptibility of children to certain drug-related adverse events. Recognition of the wide variations in drug responses in the pediatric population is sorely needed to increase the efficacy and decrease the toxicity of the drugs used beneficially with children.

Over the past two decades, gene therapy has also made important medical advances which have moved it from an early conceptual stage to provide valid treatment for certain genetic disorders, such as severe combined immune deficiency (SCID; Aiuti, 2002), muscular dystrophy (Hartigan-O'Connor & Chamberlain, 2000), and hemophilia (Hortelano & Chang, 2000). However, the remaining technical problems and the complexity and specificity of the process indicate that it still requires significant advances for widespread use of gene therapy in the near future.

In this chapter, we will give a detailed overview of pharmacogenetics and its application in identifying the relationship between genotype and drug responses to improve efficacy with young people; we will also briefly overview gene therapy as it is still at an early (but promising) stage.

BACKGROUND

The human genome comprises approximately three billion base pairs of DNA harboring 23 pairs of chromosomes. These genetic sequences are the blueprints that determine a person's physical traits and likelihood of developing certain diseases and influence the responses to therapeutic treatments. Genetic variations have been extensively observed in the human population. Of those, the most common polymorphisms (or genetic variants) in the human genome are the single-base-pair difference, i.e., single-nucleotide polymorphisms (SNPs). To date, over 10 million SNPs have been identified in the human genome. In addition to SNPs, other types of variations, such as differences in copy number, insertions, deletions, and rearrangements, occur in the human genome as well, but relatively less frequently. In terms of the function of the DNA sequence in human genome, studies have shown that only a small proportion (<5%) of the DNA sequence encodes proteins. When variations occur in these protein-coding regions, they may alter the amino acid sequence of the resulting protein and therefore change protein structure and/or function subsequently. The second proportion of DNA sequences does not encode proteins, but may have a regulatory role in influencing the gene expression level, timing, and tissue specificity (i.e., at which developmental stage and in which tissues to express the gene). The remainder of the vast majority of the DNA sequence has no known functions and is the subject of intense investigation.

Identifying the genetic variations which play a critical role in drug responses and treatments is the focus of pharmacogenetics. Uncovering

the relationship between a person's genetic makeup and drug response has significant impact because adverse drug reactions are a severe burden to the individual and to our society at large.

Drugs do not work for everyone. Studies have shown that drugs are usually effective in only 25–60% of the patients for whom they are prescribed (Spear, Heath-Chiozzi, & Huff, 2001). For one single year, 1994, a study of hospitalized patients revealed that adverse drug reactions accounted for more than 2.2 million serious cases and over 100,000 deaths, making adverse drug reactions one of the leading causes of hospitalization and death in the United States (Lazarou, Pomeranz, & Corey, 1998). A recent systematic review suggests that some of the adverse drug reactions could be prevented by modifying drug dosing or identifying patients who are at high risk of certain adverse reactions by a genetic screen (Phillips, Veenstra, Oren, Lee, & Sadee, 2001). If even a fraction of severe adverse drug reactions could be prevented, the clinical and economic benefits of pharmacogenomics may be profound (Flowers & Veenstra, 2004).

Pharmacogenetic studies hold great promises for revolutionizing the delivery of health care by integrating an individual's genetic profile into clinical decision making in order to maximize drug efficacy and minimize adverse effects. Along this direction, scientists have raised a novel concept of "personalized medicine," i.e., that a drug prescription will be tailored according to each individual's genetic profile. An outline of applying pharmacogenetic testing results to clinical practice is shown in Figure 1. Under this schema, pharmacogenetic testing results would be included

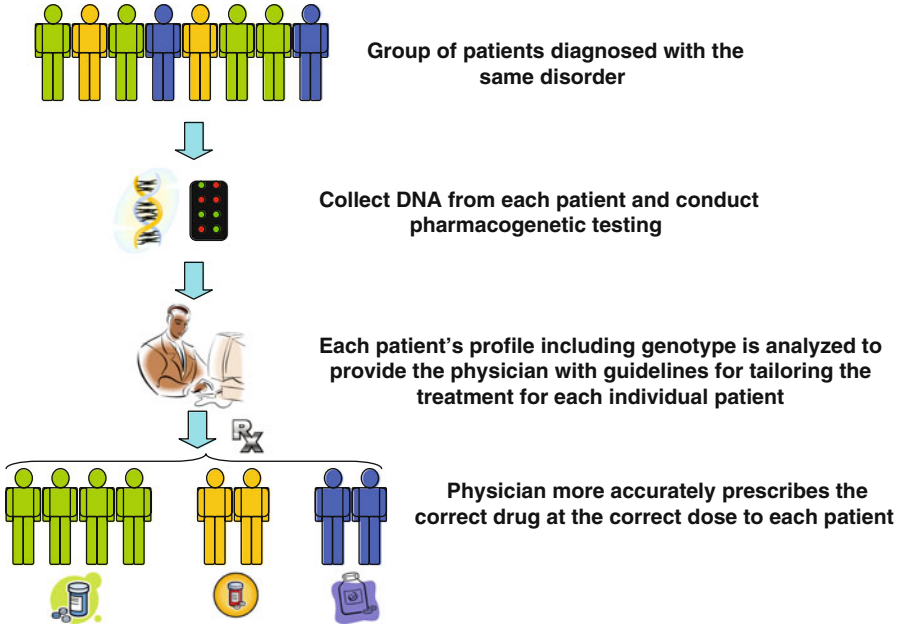

Figure 1. An outline of integrating pharmacogenetic testing results into clinical practice.

and integrated with clinical data to construct a guideline for prescribing the correct drug at the correct dose to each patient.

Pharmacogenetics is not a new field. It emerged as an experimental science in the 1950s when researchers started to explore person-to-person variability of drug responses. Researchers have found that polymorphisms in the genes that code for drug-metabolizing enzymes, drug transporters, and drug receptors can affect the efficacy of drug treatment. Molecular studies of pharmacogenetics started with the cloning and characterization of the drug-metabolizing enzyme cytochrome P450 2D6 (*CYP2D6*; Meyer & Zanger, 1997; Gonzalez et al., 1988), and *CYP2D6* remains one of the best studied polymorphic genes of pharmacological interest.

To date, more than 70 variant alleles of the *CYP2D6* gene have been identified (http://www.imm.ki.se/CYPalleles/cyp2d6.htm). These alleles are different from the wild type by one or more point mutations as well as gene deletions, duplications, or multi-duplications. The two alleles carried by an individual at a given gene locus (which is referred to as a genotype) can now be characterized by a technology called genotyping. Based on the inherited genotype at this locus, individuals can be grouped into four metabolism phenotype groups: poor, intermediate, extensive, and ultra-rapid metabolizers (Meyer, 2004). It has been found that poor metabolizers often develop adverse drug reactions, even when treated with recommended doses of a drug; in contrast, ultra-rapid metabolizers with multiple copies of *DYP2D6* genes may require higher doses of the same drug for optimal therapy (Bertilsson, Dahl, & Tybring, 1997). Obviously, if the *CYP2D6* genotype of a patient is not known, poor metabolizers could be overdosed and are at high risk of drug toxicity, whereas ultra-rapid metabolizers could be under-dosed. Interestingly, studies have found that the proportion of different metabolizers due to *CYP2D6* mutations in human population vary with ethnicity, for example, 7% of Caucasians, but only 1% of Asians, are poor metabolizers, while certain African populations (e.g., Ethiopians) have higher proportions (up to 29%) of ultra-rapid metabolizers (Binder & Holsboer, 2006). Furthermore, several population-specific alleles which are only encountered in certain ethnicities have been observed (Bertilsson, Dahl, Dalen, & Al-Shurbaji, 2002). Thus, the considerable diversity in ethnicity and ethnic origin need to be taken into consideration in pharmacogenetic studies.

The first attempt to assess pharmacogenetics as it applies specifically to children and pediatric practice was published in 1972 (Cohen & Weber, 1972). Since then, despite the remarkable progress made in understanding the basic molecular processes that result in inter-individual difference in drug responses, relatively little research that specifically relates to children has been reported (Weber, 2001). The scarcity of publications in pediatric pharmacogenetics is perhaps explained by the greater complexity, difficulty, and ethical constraints in conducting a proper pharmacogenetic study in infants and children compared with adults, rather than lack of interest or concern (Weber, 2001). Part of the complexity in the pediatric population is due to the different stages of rapid growth and development from birth to maturity. Within each stage, physiological

and biochemical attributes of cells vary to a much greater extent than at any later stage of life (Weber, 2001). Children demonstrate the same level of inter-individual genetic variability as seen in adults. Moreover, they present further differences arising from the various stages of development (Husain, Loehle, & Hein, 2007).

Below, we will give a detailed overview of current scientific findings in pharmacogenetics, highlighting the achievements in pharmacologic treatments for asthma, attention-deficit hyperactivitiy disorder, and childhood leukemia. These three conditions span the continuum of chronic and acute illness, as well as incorporate behavioral medicine components, making them particularly useful examples for our purposes.

PHARMACOGENETICS IN ASTHMA TREATMENT

Asthma, a chronic inflammatory disorder of the airways, is a very common disease associated with high morbidity and is a major public health concern. Asthma now affects 8–10% of the US population (Busse et al., 2004) and affects an estimated 300 million individuals worldwide (Masoli, Fabian, Holt, & Beasley, 2004). Review of worldwide data indicates that the prevalence of asthma has substantially increased over the past two or three decades; however, the reasons for this increasing trend are not yet clear (Keller & Lowenstein, 2002). Studies have found that there is significant individual variability in the response to asthma treatment. Even within a group of patients with an apparently identical clinical phenotype, response to drug treatment may be remarkably variable (Drazen, Silverman, & Lee, 2000). Analysis of the repeatability of asthma treatment trials, defined as the fraction of the population variance which results from among-individual differences, suggests that a substantial fraction (~60–80%) of the variance of the treatment response could be genetic in nature (Drazen et al., 2000).

Currently, glucocorticoid therapy is the primary treatment for bronchial asthma; the other two major available asthma treatments are β_2-adrenergic agonists and leukotriene inhibitors.

Asthma Steroid Pharmacogenetics

Inhaled glucocorticosteroids are the most commonly used controller therapy for asthma. However, asthma treatment with inhaled steroids varies widely between individuals (Tantisira et al., 2004). Recent studies have found that one gene, corticotrophin-releasing hormone receptor 1 (*CRHR1*), is associated with corticosteroid responses (Tantisira et al., 2004; Weiss et al., 2004). *CRHR1* is the primary receptor of corticotrophin-releasing hormone in the pituitary gland, mediating the release of adrenocorticotropic hormone, which regulates endogenous cortisol levels (Dautzenberg & Hauger, 2002; Drolet & Rivest, 2001). This evidence indicates that *CRHR1* plays a pivotal role in steroid biology.

Studies have shown that genetic variation in *CRHR1* was consistently associated with enhanced response to corticosteroid therapy in

three studied populations, as manifested by a doubling to quadrupling of the longitudinal FEV1 response (forced expiratory volume in 1 second) to corticosteroids (Tantisira et al., 2004). The change in FEV1 is a standardized and widely accepted measure of lung function; increased FEV1 indicates improved lung function. The populations examined in this study include 470 adults with asthma (termed the Adult Study), 311 children with asthma (termed CAMP, for Childhood Asthma Management Program), and another 336 adults with asthma (termed ACRN, for Asthma Clinical Research Network; Tantisira et al., 2004). The results have shown that one single polymorphic site (SNP rs242941 G/T) in *CRHR1* gene is significantly associated with corticosteroid response after 8 weeks in the Adult Study and CAMP populations. Individuals with the TT genotype demonstrated at least a doubling of the improvement in lung function with corticosteroid use compared with the patients with the GG genotype (Tantisira et al., 2004). Another polymorphic site (SNP, rs1876828 A/G) in the same gene *CRHR1* was significantly associated with the response after 6 weeks in the ACRN population. Individuals with the AA genotype showed a quadrupling of improvement in lung function with corticosteroid use compared with the patients with the GG genotype (Tantisira et al., 2004). These results collectively indicate that genetic variants in *CRHR1* gene have pharmacogenetic effects influencing response to corticosteroids.

β_2-Adrenergic Receptor Gene in Asthma Treatment

Among the sources of variability that contribute to the heterogeneity in the response to asthma treatment, another example comes from studies on the human β_2-adrenergic receptor gene. The β_2-adrenergic agonists, such as albuterol, are the most commonly used therapy for quick relief of asthma symptoms in clinical practice. These medications act by stimulating the β_2-adrenergic receptor (*B2AR*) to relax smooth muscle resulting in subsequent bronchodilation.

B2AR is a highly polymorphic gene for which 13 SNPs have been identified within a span of 1.6 kb, containing the promoter and coding regions of the gene (Drysdale et al., 2000). One SNP at the coding region of *B2AR* gene which alters the amino acid at position 16 (from Arg to Gly) has been reported to be associated with responses to inhaled albuterol in a pediatric group of 269 children around 11 years old. In this study, spirometry was performed before and 30 min after the administration of 180 μg of albuterol, and a positive response was considered with an increase of >15.3% predicted FEV1 (Martinez, Graves, Baldini, Solomon, & Erickson, 1997). After adjusting for asthma and wheezing status, the results revealed that children who are homozygous for the Arg-16 allele (Arg/Arg) were 5.3 times, and heterozygotes (Arg/Gly) 2.3 times, more likely to show a positive response to albuterol therapy than homozygous for the Gly-16 allele (Gly/Gly; Martinez et al., 1997). In this study, parents were instructed to stop any bronchodilator therapy 6 h before the scheduled time for the albuterol test; thus, the results obtained herein may explain some of the variability in response to albuterol therapy in this group of children (Martinez et al., 1997).

In addition, another study has examined the effect of the combination of the 13 identified SNPs of *B2AR* gene at haplotype level (adjacent SNPs that are inherited together are compiled into haplotype in the human genome) on bronchodilator response (Drysdale et al., 2000). In this study, a group of 121 Caucasian adult patients with asthma were recruited; patients underwent spirometry before and 30 min after inhalation of 180 μg of albuterol delivered by nebulization. The change in the percentage predicted FEV1 was considered the primary measure of responses to albuterol (Dales, Spitzer, Tousignant, Schechter, & Suissa, 1988). The 13 SNPs were found organized into 12 haplotypes (numbered from 1 to 12) in this group of patients. Remarkably, patients carrying different haplotype pairs demonstrated significantly different improvements in FEV1, where individuals with haplotype pairs (#4 and #6) had the highest response (change percentage FEV1 = 19.1 ± 2.79) and individuals with haplotype pairs (#4 and #4) had the lowest response (change percentage FEV1 = 8.53 ± 1.78). Taken together, these results suggest that genetic variations in β_2-adrenergic receptor gene may contribute to the albuterol response to asthma.

Leukotriene Response in Asthma Treatment

It has been found that clinically similar patients with asthma may develop airway obstruction by different mechanisms (Barnes, 1995; Lemanske & Busse, 1997). The third major approach to treat asthma, interfere with the 5-lipoxygenase (*ALOX5*) pathway, may be an option when products of the *ALOX5* pathway (the leukotrienes) contribute to the expression of the asthma phenotype (Drazen et al., 1999). Studies have found that genetic variant, specifically the tandem repeats of the Sp1-binding motif (GGGCGG) at the promoter region of *ALOX5* gene, correlated with responses to ABT-761 treatment – a potent and selective inhibitor of *ALOX5*. The most common allele at this locus contains five tandem repeats of this motif in the population (referred as wild type; Drazen et al., 1999). The results have shown that individuals who received active ABT-761 (interferes with the *ALOX5* pathway) treatment, who are homozygous for wild type, or heterozygous had an improvement in FEV1 after 1 week of treatment and at the completion of the trial (12 weeks). The average change in FEV1 at the end of the active treatment period was 18.8% in wild-type patients and 23.3% in heterozygous patients. By contrast, patients with altered alleles (carrying three or four tandem repeats of the motif at both chromosomes) had no benefit from active treatment, as measured by an average change in FEV1 of –1.2% (Drazen et al., 1999). These results provide more evidence supporting genetic variants of a therapeutic agent target that can be used to predict clinical response to treatment.

In addition, a multi-center, randomized, and double-masked clinical trial designed to determine the long-term effects of treatments for mild to moderate childhood asthma, the Childhood Asthma Management Program (CAMP) is ongoing (Childhood Asthma Management Program Research Group, 1999). Genetic polymorphisms related to the responses of asthma treatment continue to be evaluated among children in the CAMP study.

We optimistically expect that more solid pharmacogenetic results related to pediatric asthma treatment responses will be forthcoming.

Pharmacogenetics in Attention-Deficit Hyperactivitiy Disorder

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood characterized by age in appropriate levels of inattention, hyperactivity, and impulsivity, with an estimated worldwide prevalence of ~7–17% among school-aged children (Kanbayashi, Nakata, Fujii, Kita, & Wada, 1994; Szatmari, Offord, & Boyle, 1989; Wolraich, Hannah, Pinnock, Baumgaertel, & Brown, 1996). Twin studies indicate that the heritability of ADHD is 70–95% (Gillis, Gilger, Pennington, & DeFries, 1992; Sherman, Iacono, & McGue, 1997; Sherman, McGue, & Iacono, 1997; Stevenson, 1992; Thapar, Hervas, & McGuffin, 1995), suggesting that genetics plays a critical role in the development of ADHD. Pharmacogenetic studies in ADHD suggest that most inter-individual differences in response to stimulant medication therapy may be related to underlying genetic influences (Husain et al., 2007; Kirley et al., 2003; Hamarman, Fossella, Ulger, Brimacombe, & Dermody, 2004).

Among the pharmacogenetic studies in ADHD disorders, *DAT1* (dopamine transporter gene) is a particularly relevant candidate gene because the dopamine transporter is the action site of the stimulant medications used in the treatment of ADHD (Seeman & Madras, 1998). Experiments from animal models have demonstrated that knockout mice lacking the *DAT1* gene are extremely hyperactive (Caron, 1996; Giros, Jaber, Jones, Wightman, & Caron, 1996). In a pioneering study, Winsberg and Comings reported decreased methylphenidate (MPH, a treatment for ADHD) response in a group of African-American children homozygous for the 10-repeat (480 bp) allele of a variable number tandem repeat (VNTR) in the 3′-untranslated region of *DAT1* (Winsberg & Comings, 1999). In this study, 30 African-American children who were diagnosed with ADHD were included on MPH treatment. Of these 30 patients, 14 were non-responders and 16 were responders based on standard criteria. Interestingly, 86% of the non-responders were homozygous for the 10 copy allele, compared with 31% in responder groups ($p = 0.008$). Later, the association result between homozygosity for the 10-repeat allele in *DAT1* gene and poor response to MPH treatment was confirmed in an independent study of a group of Brazilian patients of European descent ($n = 50$; Roman et al., 2002). Although there were several other studies that found no effect of *DAT1* polymorphism with ADHD treatment (Hamarman et al., 2004; Langley et al., 2005; van der Meulen et al., 2005), the inconsistent results might be due to a lack of standardized clinical outcome, small sample size, and/or little consideration given to potential covariates, such as presence or absence of other psychiatric disorders. Obviously, large prospective studies are needed to examine and confirm the role of genetics in ADHD treatment response.

Emerging evidence has identified other candidate genes that may play a role in ADHD medication response (Husain et al., 2007; McGough,

2005). Researchers have noted that the 7-repeat (48 bp) VNTR polymorphism in the coding region of *DRD4* (dopamine receptor gene) produces blunted responses to dopamine (Asghari et al., 1995; Van Tol et al., 1992). One or two copies of the 7-repeat necessitated higher MPH doses for optimal symptom reduction, i.e., subjects with the 7-repeat allele required 1.5 times more MPH than subjects without the 7-repeat alleles (Hamarman et al., 2004).

Variation in MPH response has also been shown to be associated with a G1287A polymorphism in the norepinephrine transporter gene (Yang, Wang, Li, & Faraone, 2004). More recently, the adrenergic α-2A receptor gene (*ADRA2A*) was studied in response to MPH as well (Polanczyk et al., 2007). These results collectively suggested that pharmacogenetic studies on ADHD are encouraging, though preliminary studies have been limited by small sample size. Future studies which emphasize large, prospective trials have been proposed. The larger sample size also allows the investigators to examine gene–gene interactions and potential covariates in ADHD treatment. Utilizing the knowledge gained from these studies in clinical practice holds the potential for optimized, individualized therapies for patients with ADHD in an emerging era of personalized behavioral medicine.

Pharmacogenetics in Childhood Leukemia

Acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells, the cells in the body that normally fight infections. Cancer in children and adolescents is rare, but ALL is the most common form of pediatric cancer, representing 15–30% of all childhood malignancies (Krajinovic et al., 2002). It is characterized by the predominance of lymphoblasts or immature hematopoietic precursors, with malignant cells expressing diverse phenotypes and variable response to chemotherapy (Pui, 2000; Camitta, Pullen, & Murphy, 1997). Treatment involving multiple chemotherapeutics has led to a remarkable improvement in disease outcome. However, 20–40% of patients develop resistance to current therapeutic protocols (Pui, 2000; Chessells, Bailey, & Richards, 1995). Intensive treatment also has significant long-term consequences, causing secondary malignancies and cognitive impairments. Therefore, it is necessary to identify factors associated with both the risk of relapse and drug side effects.

Many studies have investigated the relationship between genetic variants and cancer therapy response. Among these, 6-mercaptopurine (6-MP) is one of the key medications for treatment of ALL and can be catalyzed by thiopurine methyltransferase (*TPMT*; Husain et al., 2007). *TPMT* activity in humans is inherited as an autosomal co-dominant trait; patients who are heterozygous at the *TPMT* gene locus are at intermediate risk of dose toxicity (Krynetski & Evans, 1998). Numerous studies have consistently shown that patients with *TPMT* deficiency, i.e., homozygous for the variant allele, are at very high risk of severe hematopoietic toxicity if treated with conventional doses of thiopurines (Evans, Horner, Chu, Kalwinsky, & Roberts, 1991; Lennard, Lilleyman, Van Loon, & Weinshilboum, 1990).

TPMT-deficient patients with ALL tolerated full dose of 6-MP for only 7% of the scheduled weeks of therapy; whereas *TPMT* heterozygous and *TPMT* homozygous for wild-type patients tolerated full doses for 65 and 84% of the scheduled weeks, respectively (Husain et al., 2007). These data suggested that the dose of 6-MP should be adjusted to patients with *TPMT* deficiency and those who are heterozygous. Studies have shown that the *TPMT*-deficient patients actually required a mean dose reduction of 90%, and the *TPMT* heterozygotes required a mean dose reduction of 35% (Husain et al., 2007). It has been known that approximately 10% of Caucasian and African-American populations are heterozygous for *TPMT*, and approximately 1 in 300 inherit *TPMT* deficiency (Krynetski & Evans, 1998). The impacts of pharmacogenomic research have already started to greatly enhance the safety of treating children diagnosed with ALL, as *TPMT*-deficient individuals can be easily identified. These advances, together with the fast developments in biotechnology, are paving the road for a new era in the practice of personalization of health care.

Translation and Challenges in Pharmacogenetics

The achievements of pharmacogenetics have started to improve clinical practice, deliver benefits to improve public health care, and maximally avoid adverse drug reactions. Several confirmed pharmacogenetic results have been integrated into clinical practice and serve as a guideline for optimizing treatment responses.

Warfarin is prescribed to over 1 million patients annually in the United States, making it the most commonly used oral anticoagulant and the primary agent for treatment of thromboembolic events (Krynetskiy & McDonnell, 2007). The correct maintenance dose of warfarin for a given patient was difficult to predict because the safe dose range differs widely between individuals. Warfarin-associated adverse drug reactions, such as bleeding, are common. A recent study found that warfarin accounted for 10.5% of the adverse drug reaction cases in hospital admissions in the United Kingdom, making it the third most common drug to account for this (Pirmohamed et al., 2004).

To date, approximately 30 genes have been found that contribute to the therapeutic effects of warfarin, and genetic polymorphisms in these genes may modulate its anticoagulant activity. The strongest predictors were two genes: cytochrome P450 2C9 (*CYP2C9*) and the vitamin K epoxide reductase complex subunit 1 (*VKORC1*). Warfarin is metabolized by *CYP2C9* and exerts its anticoagulant effect by inhibiting *VKORC1*. Genetic variants of the *CYP2C9* gene are associated with decreased warfarin clearance, resulting in increased half-life and time to reach stable therapy. Studies have shown that genetic variants of *VKORC1* decrease the warfarin dose requirement necessary to achieve effective anticoagulation. Notably, pharmacogenetic testing revealed that inherited combined variants of *CYP2C9* and *VKORC1* account for approximately 40% of warfarin dose variability (Reynolds, Valdes, Hartung, & Linder, 2007). In 2007, the FDA updated the product label for warfarin to include genetic variations in *CYP2C9* and *VKORC1* as one of the factors to consider for more

precise initial dosing (Ndegwa, 2007), though the impact of the inclusion of genetics in warfarin dosing on long-term health outcome and its cost-effectiveness remains to be seen.

Evidence from other disease treatments has also demonstrated that understanding pharmacogenetics can lead to clinical benefit. For example, estrogen receptor and progesterone receptor are used to select patients with breast cancer who are more likely to respond to hormone therapy (Duffy, 2005). A more recently introduced predictive marker is *HER-2* for selecting patients with advanced breast cancer for treatment with the therapeutic antibody trastuzumab (Hereptin; Smith et al., 2007).

Despite these fruitful achievements, there are challenges in the pharmacogenetics field. One major issue is whether the relationship between genotype and phenotype, such as some enzyme activities, obtained from the normal population will still hold true in the disease population. *NAT2* (*N*-acetyltransferase 2) is an enzyme and functions to both activate and deactivate arylamine and hydrazine drugs and carcinogens. Polymorphisms in *NAT2* can be used to segregate the human population into rapid, intermediate, and slow acetylator phenotypes. In a cross-sectional study, 105 patients who were positive for HIV and patients with acquired immunodeficiency syndrome (AIDS) were phenotyped for *NAT2* activity with the use of caffeine as an in vivo probe. Remarkably, there were 18 discrepancies between genotype and *NAT2* activity (phenotype) observed in these patients with HIV infection and AIDS, i.e., 12 slow acetylators with fast genotypes and 6 fast acetylators with slow genotypes. Furthermore, among patients with *NAT2* activity being phenotyped more than once (mean time between samples, 10.4 months), changes in *NAT2* activity phenotype from fast to slow were associated with progression of HIV infection (O'Neil, Gilfix, DiGirolamo, Tsoukas, & Wainer, 1997). These results highly suggested that disease progression in HIV infection and AIDS may alter expression of the *NAT2* gene.

In addition, there are challenges especially for delivering pharmacogenetics into clinical pediatrics. Applying pharmacogenetic results derived form adult studies may have limited applicability to pediatric disease, for example, because disease processes affecting newborn infants such as patent ductus arteriosus, or diseases of childhood such as Kawasaki's disease, have no close correlates in adults (Leeder & Kearns, 2002). Additionally, several diseases with complex etiologies such as asthma, autism, ADHD, juvenile rheumatoid arthritis, and type 1 diabetes have their origins during childhood and are associated with age-related differences with respect to drug delivery, dosing, and therapeutic response as compared to adults (Leeder & Kearns, 2002).

Pediatrics is one of the most rapidly growing prescription markets in the nation. Compared to adult patients, children have developmental differences in the absorption, metabolism, and distribution of drugs. Adult studies do not address the potential effects of drugs on growth and development. Although the genome is constant across the life span, expression patterns change markedly during growth, making pharmacogenetics more of a challenge in pediatrics than it is in adult medicine (Lipshultz, 2005). Furthermore, there are challenges for those conditions

where the etiologies are poorly understood, and as a consequence, the basis for pharmacotherapy is least evident. Moreover, the ethical, legal, and social issues related to genetic testing in children have not been completely resolved. All of these challenges require extensive scientific research in pediatric populations and enhanced and continuous education to clinical practitioners, parents, and patients for developing effective strategies to improve pediatric patient care.

Gene Therapy

The concept of transferring genes to tissues for clinical applications has been discussed for nearly half a century, but our ability to manipulate genetic material via recombinant DNA technology has brought this goal to reality (Cotrim & Baum, 2008). Over the past decades, gene therapy has made important medical advances. It has moved from the conceptual stage to technology development and from laboratory research to clinical translational trials for a variety of diseases.

Adenosine deaminase (*ADA*)-deficient severe combined immunodeficiency (SCID) was the first inherited disease successfully treated with gene therapy (Aiuti, 2002). Affected children are born without an effective immune system and thus will have infections from outside contact. About 25% of the patients with SCID are the result of the child being homozygous for defective genes encoding the enzyme *ADA*. A landmark study for this disease was conducted by investigators in Italy, who successfully cured the disease through bone marrow transplantation from matched donors (Bordignon et al., 1995).

Gene therapy for muscular dystrophy (MD) has also made encouraging progress though is facing significant challenges, including the large amount of muscle tissue in the body (muscle tissues make up more than 40% of body mass), the large size of many genes defective in different muscular dystrophies, and the possibility of a host immune response against the therapeutic gene (Hartigan-O'Connor & Chamberlain, 2000). Over the past decades, tremendous progress has been made in developing improved viral vectors and avoiding immune reactions against gene transfer (Chamberlain, 2002). Numerous vectors are now available to transducer muscle tissues with minimal immunological or toxic side effects (Chamberlain, 2002). The advances in this field suggest that barriers to gene therapy for MD may be surmountable.

Hemophilia A and B are X-linked genetic disorders caused by deficiency of the coagulation factors VIII and IX, respectively. Patients born with hemophilia are not able to induce blood clots and suffer from external and internal bleeding that can be life threatening. The first challenge in developing successful gene therapy is to find the right vector to deliver the factor VIII- and IX-producing genes to the cells. The efficacy of this approach has been limited due to immune responses against the viral components. Recently, an alternative approach has been proposed to use physical methods such as in vivo electroporation to deliver plasmid DNA, thus avoiding some of the complications associated with viral-based delivery systems (Fewell, 2008). Such progress in gene therapy, especially for

hemophilia B, has been promising and is likely to reach clinical trial in the foreseeable future (Hortelano & Chang, 2000).

Gene therapy was originally conceived of as a way to treat life-threatening disorders, such as inborn errors and cancers. The common feature of these disorders is that they are caused by a defect of a single gene. Gene therapy is now considered for many non-life-threatening conditions, such as for Parkinson's disease (Nakano, 2008). Despite many technical challenges, gene therapy has made substantial progress, though relatively slower than initially predicted.

APPLYING PHARMACOGENOMICS IN MEDICATION MANAGEMENT FOR PEDIATRIC CHRONIC CONDITIONS: PSYCHOLOGICAL ASPECTS

Scientific data concerning pharmacogenetics and pharmacogenomics have the potential to enhance the impact of medical treatment on relevant clinical outcomes through a targeted, personalized approach to medication management (Boat, 2007). Although the scientific advances discussed in this chapter have not yet been fully translated into clinical care, it is important to anticipate the issues that will need to be addressed in order to implement such approaches and evaluate their impact. Toward this end, several key challenges will be important to consider and anticipate. These include involving families in decision making concerning personalized treatment based on pharmacogenomic information, developing approaches to monitor clinical outcomes, and engaging families in adherence promotion and evaluation of treatment adherence. These issues are addressed below.

INVOLVING FAMILIES IN DECISION MAKING REGARDING PERSONALIZED TREATMENT

Similar to other applications of new technologies that use genetic information to guide medical care (Miller, McDaniel, Rolland, & Feetham, 2006; Patenaude, 2005), clinical applications of pediatric pharmacogenomics will need to involve families in communication and decision making to initiate changes in pharmacological treatment based on an individualized treatment approach (Makoul & Clayman, 2006). Clinical management based on pharmacogenomics will most likely take place in the context of research that is studying the effect of different medications for children with chronic behavioral and physical conditions who have specific genetic profiles.[81, 82] For example, patients with severe side effects or intractable conditions may be identified who may benefit from a targeted approach to medication management that is informed by genetic data (Froehlich, McGough, & Stein, in press; Glauser, 2007). Glauser and colleagues (2007) have described the identification of genomic patterns that underlie adverse side effects in pediatric epilepsy such as valproic

acid-associated weight gain. Because the side effects of medications are likely to be relevant to clinical decision making and important to patients and their families, it would be helpful to use structured and well-validated approaches to obtain information concerning child and parental beliefs about medication and understanding of side effects (Conn et al., 2005; Riekert & Drotar, 2002).

In order to promote the most effective application of pharmacogenomic data to clinical management, practitioners will also need to communicate effectively with families concerning the following issues: the need to obtain genetic data, how this information will be used to guide medication management, and parent and child expectations concerning the targeted approach to medication. Toward this end, parents and children should benefit from a clear explanation of how information from genetic data is expected to facilitate medical management (e.g., by enhancing the effectiveness of pharmacological treatment and/or by reducing side effects).

Another question that will be important to children and families is how the efficacy of medication that is targeted on the basis of genetic data will be monitored and how additional changes in the medication management will be made. Encouraging active family participation in the monitoring of impact of medication treatment on clinical outcomes will be helpful in evaluating the impact of the treatment, making necessary changes and encouraging family participation in follow-up. For example, families can be involved in providing valuable data concerning the frequency of symptoms or illness control (Yawn, Brenneman, Allen-Ramey, Cabana, & Markson, 2006) as well as the functional impact of symptoms based on valid methods that have been designed for this purpose (Palermo et al., 2008).

ENGAGING FAMILIES IN ADHERENCE PROMOTION

For maximum effectiveness of prescribed medication treatment based on genetic data, children and families should be actively engaged in adherence promotion efforts as part of their medical management. For example, children and families need to understand that even though the new medication treatment may have more powerful and/or targeted effects, it is critical that they take the medication exactly as prescribed in order for maximal clinical benefits to be realized. The prevalence of nonadherence to many medications used to treat chronic physical and behavioral conditions is very high (Rapoff, 1999; Drotar, 2000). For this reason, one can anticipate that nonadherence will be a significant problem even for medications that are found to be effective or have reduced side effects based on genetic data. For this reason, children and families will need support using effective behavioral method (Kahana, Drotar, & Frazier, 2008) to help them adhere to new medication treatments that are prescribed. Families may also have high expectations for new medications and need support to sustain their adherence if the clinical benefits of medications turn out to be less than optimal or expected.

EVALUATING TREATMENT ADHERENCE IN RESEARCH AND CLINICAL CARE

Objective data concerning treatment adherence are very important from the standpoint of evaluating the response of new medications that are targeted to a child's genetic profile. No matter how potentially effective a medication is, it will not be maximally effective and will lose potency to the degree that it is not taken. Moreover, it is difficult if not impossible to obtain accurate data concerning the level of exposure of a new targeted medication in the absence of detailed information concerning dosing history and adherence (Vrijens, Gross, & Urquhart, 2005; Kenna, Labbe, Barrett, & Pfister, 2005). For this reason, it will be important to include a specific plan for assessment of adherence to treatment in the child's medical management as well as in research on protocols that evaluate effectiveness of medications.

Methods that are available to assess child and family adherence to medication treatment range from readily available approaches, such as self-report pill counts or pharmacy records, to more objective but expensive methods such as bioassay and electronic monitoring that provide detailed records that can be used for research (Rapoff, 1999). Various assessments of adherence to treatment have different costs and benefits (Rapoff, 1999). However, even self-report, which is not an ideal method owing to potential for bias, has validity to detect nonadherence that is reported (Bauman et al., 2002). Moreover, novel and objective methods such as bioassays have shown promise in monitoring adherence in the context of clinical care. For example, the standard deviation of tacrolimus levels has shown promise in detecting clinically significant nonadherence to medication treatment in liver transplantation (Venkat, Nick, Wang, & Bucuvalas, 2008).

CONCLUSION

Since the completion of the Human Genome Project, scientists have learned much about human genetic variation and its application in pharmacogenetics. To date, pharmacogenetic studies have been conducted on almost every pharmacotherapeutic treatment. Advances in pharmacogenetics have begun to shape the way in which medicine is practiced.

Despite the considerable challenges, pharmacogenetics holds the potential to improve therapeutic effectiveness and minimize toxicities of the drugs. In the next decade or two, it is likely that pharmacogenetics will continue to expand, and it may become common practice to screen the entire population or specific subgroups for genetic information in order to improve drug safety and efficacy for each individual patient. In terms of long-term health outcome, there is a clear need for prospective studies to demonstrate the cost-effectiveness of applying pharmacogenetics in clinical practice.

Toward personalized medicine, drug prescribing and dosing would no longer be "one size fits all," but would be carefully tailored to take a patient's individual genetic profile into consideration. The understanding of an individual's genetic variants and his/her drug responses will provide physicians with additional key information. Together with other important factors such as clinical manifestation, lab results, and environmental exposures (i.e., environmental smoke exposure, diet), pharmacogenetics adds to the knowledge necessary to guide physicians in prescribing the right drug at the right dose to the right patient.

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Informed Consent and the Protection of Human Subjects in Genomic Research with Children and Families

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Consideration of the ethics of genetic testing of children under research auspices is complex under any circumstances. Because of contemporary issues that affect such analysis, any attempt to parse the topic must be very exacting. Such issues include the following:

- the increasing volume of pediatric research, which will presumably lead to an increase in genetic research in this population;
- the ongoing debate in genetics research about the obligations of researchers to share the individual results of molecular testing with subjects (and presumably, families, when such subjects are children);
- how to best understand the data that has come from studies about the possible harms to individual children of receiving genetic testing results; and
- the best ways to apply traditional bioethical analysis about participation of children in clinical research to enrolling children in such studies that include genetic testing.

All of these issues impact the ways that investigators should approach the enrollment process for children into genetic studies. Discussions within this chapter will address how each topic must be conceptualized

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as the expected increase of pediatric research studies that include molecular genetic testing provides the research community with challenges to adequately inform parents and children about the implications of enrolling in such studies.

PEDIATRIC RESEARCH INITIATIVES

With the renewal of the Best Pharmaceuticals Act for Children by the US Congress (Maloney, 2007), a 10-year effort to increase the amount of pediatric research has been given an impetus to continue toward the goal of enrolling more subjects under the age of 18 years. Two specific governmental mechanisms have been used to spur this effort. One is the 1998 National Institutes of Health (NIH) policy guidelines about the inclusion of children (defined as people under 21) in sponsored research studies. The single goal of this policy was "... to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children" (http://grants.nih.gov/grants/guide/notice-files/not98-024.html). Accordingly, applicants for NIH-sponsored grants and contracts now must address instructions in their applications about such inclusions that mirror earlier mandates about the incorporation of women and minorities in research studies. The second governmental effort involved executive and legislative actions.

In August 1997, President Clinton and Health and Human Services Secretary Shalala proposed 21 CFR Parts 201, 312, 314, and 601, entitled *Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients* (http://www.fda.gov/cder/guidance/pedrule.htm). These new provisions were intended to require drug manufacturers prior to marketing any new pharmaceuticals, not just those intended for children, to test such drugs for safety and effectiveness in children. Before the 1997 proposal could be commented on and implemented, the *1997 FDA Modernization Act (FDAMA)* was passed by the 105th Congress and signed into law. This legislation directed the FDA, in concert with pediatric medical experts, to draft a list of those drugs already approved for adults for which pediatric studies would provide health benefits to children. Drug companies that held patents on approved drugs that were determined to have definite implications on pediatric health were offered 6-month extensions on their patents on such drugs, if they conducted further testing of the drugs for pediatric use. The *Food and Drug Administration Amendments Act of 2007* (*FDAMA, 2007*) continues the program of patent extensions by reauthorizing the specific programs that govern this initiative under the auspices of the Best Pharmaceuticals for Children Act and The Pediatric Research Equity Act (http://www.fda.gov/oc/initiatives/fdaaa/PL110-85.pdf).

There was an immediate expectation that the numbers of children in research would increase as these programs were put into place (Ross, 2003b). The impact of these two efforts to increase the numbers of children in research is unclear. Neither the NIH nor the Food and Drug Administration, which is charged with implementing oversight of drug

research, has estimates on how many more children have been involved in research since these strategies have been employed. Discussions about their effects have focused mostly on highlighting the potential ethical issues that increased pediatric research may produce (Hull, Glanz, Steffen, & Wilfond, 2004; Kopelman, 2006; Koren, 2003).

Equally unclear are the implications of these policies for increasing enrollment of children in research that involves collecting genetic material. The only mention of genetic testing in the FDAMA 2007 addresses the development of safety guidelines for genetic testing, not about who will be tested. However, it appears that all types of clinical research trials, including those enrolling children, have started collecting biologic material for examination of DNA for possible links to phenotypical and other data, such as behavioral and psychosocial data (Hull et al., 2004).

Genomic alterations that may be linked with risk for disease are important foci of translational research, and it is critical for such research to link basic genetic information to genomic health data. The processes by which parents perceive and consider risks and benefits when giving permission for their children to be enrolled in genetics research are not well understood (Burke & Diekema, 2006).

Current regulations governing pediatric research derive from ethical principles developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research synthesized in the Belmont Report. Research with children poses unique ethical questions about the special protections necessary when varying levels of risk are possible. This is due, in part, to the diminished autonomy of the child that makes them especially vulnerable to risks in research that are difficult to quantify (Collogan & Fleischman, 2005). Additionally, parents may not fully appreciate the risks inherent in research, thereby limiting their ability to protect their children.

While there has been much discussion about involving parents in the general research permission process based on the varying levels of risk in a given type of research, studies have not been reported that analyze the decisions of parents during the enrollment process in genetic studies. Much genetic testing is conducted in clinical practice for the purposes of determining risk for oneself and/or one's offspring, diagnosis, and, in some cases, treatment decisions. However, significant amounts of genetic testing occur under the auspices of research, and the pace of movement from research to clinical application can vary with each clinical situation. Parents are a crucial part of the protective process when children are solicited into any type of research (Rubenstein, 2003), but little is known about how parents interpret their role when making the decision to allow their child's enrollment in genetic studies.

THE BIOETHICS OF PROTECTION OF CHILDREN IN CLINICAL RESEARCH

Ethical analysis of enrolling children in genetic research needs to take into account current practices for enrolling children into any clinical research protocols. Then the determination of how parents and

researchers should consider including genetic testing in pediatric protocols can be better established. When involvement of children in any pediatric research is contemplated, two primary issues must be considered. One is the necessity of including children in trials so that they, as a group or as individuals, may reap the benefits of research while sharing its burdens. This, essentially, is a justice perspective. The second is how to protect children when they are enrolled as subjects.

Historical Perspectives

The moral framework of research protection for children derives from the Belmont Report, is institutionalized by SubPart D of 45 CFR 46 in federal law, and bases its ethical grounding around protecting children by defining parental responsibility and rights (Field & Behrman, 2001). Special considerations were made by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1977) which considered the use of children in research. Levine (1986) reported that the National Commission took the position that infants and young children have no true autonomy and that protection of their personhood is essentially physical protection from harm.

The Commission faced many arguments about the concept of pediatric autonomy as well as the reality that to forbid research of either a beneficial or non-beneficial purpose would halt necessary inquiry into childhood health concerns. Children then would be what Robert Levine terms "therapeutic orphans" (1986, p. 239). His term refers to a population that suffers from true health problems that are ripe for inquiry but goes uninvestigated. The effect of therapeutic orphan status is that children either are given drugs and subject to interventions that have gone untested in pediatric samples (Kodish, 2005) or are only investigated informally with already ill children, thus imposing a further burden on a disadvantaged child.

In recommending that children be included in research supported by the federal government, the Commission accepted that such inquiry was essential and that the key to involving children in any research, but particularly in research that is of no therapeutic worth to the individual, is protection of the child. While there was no discussion of the involvement of children in genetic research during this epoch of ethical consideration, there is no reason to believe that the ethic of protection of children would be subsumed to other considerations when they are asked to provide genetic material.

Enrollment of Children in Research

The Child's Role in the Research Enrollment Process

The challenge of pediatric enrollment involves both the parental and the child's role in deciding personally whether or not to participate in a clinical trial. In ethical lexicon, *consent* refers to a process that involves

competency, a legal concept, and capacity, which is a psychological judgment. A determination of capacity generally requires that the decision maker can understand the nature and goals of the proposed procedure, whether research or therapeutic in nature. The consent process requires that the competent person be able to freely decide whether or not to participate. The National Commission (1977), in Recommendation Seven, proposed that in pediatric research, parents of child subjects must consent to participation of their child and those children seven and older must *assent* to enrollment. Assent is different from consent not only because the former lacks the legal status of consent but because it also lacks the critical element of consent – that of the crucial power to dissent. The eventual regulations adopted by the Department of Health and Human Services left the age of assent up to the individual IRB evaluating a discrete protocol (Reed, 1999).

While assent has less legal standing than consent, it is a morally powerful concept, for it requires that investigators present their proposed research to a possible child subject in a developmentally appropriate fashion. Not only does this mandate the use of language that a child can comprehend but it also requires that investigators and IRBs consider the psychological and developmental responses that varied age groups will manifest when approached by an adult to do something – e.g., unquestioned acquiescence, determination to please, guilt over rejection – and provide supports for a child so that he or she can respond in a way that maintains his or her dignity (Koocher & Keith-Spiegel, 1994).

Capacity issues. The informed consent process is an educational procedure consisting of many parts that the researcher must guide the prospective subject through. There appears to be no valid reason to exclude children of school age and older from the decision-making process about research participation. Multiple studies have examined varied aspects of children's decision-making capacity in health-care decisions (Miller & Nelson, 2006). While specific aspects of children's decision-making capacity have been examined, in general, the conclusion has been that young children from the age of 7 can participate meaningfully in determinations about their health and that capacity increases with both age and experiences relevant to those decisions, like past medical care. Considerations about children's capacity to assent and dissent are critical as researchers begin approaching healthy children to participate in drug studies. If part of the benefit of being a volunteer is the rewards of altruism, then children must have the opportunity to appreciate the value of their gift of volunteerism through the assent/consent process.

Though researchers will probably enroll children in research protocols based on their physical age, pediatric clinicians and developmental specialists realize that psychological development is the best means of assessing the child's ability to validly agree to cooperate with any research study (Broome & Stieglitz, 1992). This requires an understanding of how children in different developmental stages will interpret the research encounter (Baylis, Downie, & Kenny, 1999). While children in the

preschool years cannot usually move beyond their personal experiences to generalize to abstract options, older children from 7 to 12 are considered to be capable of enough critical thinking to participate in personal decision making about concepts such as altruism and therefore should be asked about their preferences about research participation (Miller, Reynolds, & Nelson, 2008).

As children enter adolescence, their input into any types of research, therapeutic and nontherapeutic, should be as strongly considered in the research enrollment process as that of the parents, though parental permission is still usually required. In nontherapeutic research, most agree that older adolescents should have a strong say in the decision and in some cases parents do not even have to be approached (Broome, Kodish, Geller, & Siminoff, 2003). In fact, requiring parental permission for adolescents to take part in studies such as risk behavior surveillance surveys has been conjectured to lower intended participation by teens from 93–100% to 30–60%, with a projected cost of $20–25 per subject to recontact the families to try and persuade parents to allow their child's involvement (Tigges, 2003).

This issue of considering possible dissent becomes crucial when the question of including healthy children in research which provides no direct benefit to them becomes a possibility. Children are a vulnerable population, particularly because in all of their developmental stages, there exists a strong propensity for children to be coerced into participation, primarily because of the need to please their parents or other adult authority figures, such as medical/scientific personnel (Rhodes, 2005). Additionally, coercion can occur for more subtle reasons, such as when monetary incentives are offered to either the child or family to participate and continue in a trial (Diekema, 2006). It is also suggested that children who dissent from participation should have their concerns considered and addressed before enrolling them against their will (Masty, 2008), whether it be therapeutic or nontherapeutic research.

Assent and dissent in genetic research. The ability of young children to participate in the enrollment process in genetic studies is hard to assess. There is little data to suggest that children appreciate the genetic aspects of being in a study any more or less than other parts of a complex project such as a research protocol. Because of the nature of genetic information to have future implications for a child's health, it is reasonable for the parental role in genetic research to be emphasized, particularly when younger children, under the age of 10 years, are solicited (Burke & Diekema, 2006). However, it becomes problematic when a younger adolescent decides to decline the genetic aspect of a study that might be useful to another member of the family. The example of a family undergoing linkage analysis to track a possible disease link through its pedigree might not be appreciated by a child who has a sense of privacy and decides his needs are greater than that of the family for information. In this case, the researcher and family might want to understand that such a dissent should be honored and that any further efforts at persuasion should focus on education, not coercion.

Parental Decision Making and Research

Parents are expected to only expose their children to minimal risks that are justified by the possible benefits of the research. However, this moral theory of beneficence has flaws when applied to non-beneficial pediatric research (Nelson, 2005). Though parents may chose altruism as a basis for personal enrollment in a research study, selflessness can be asked of a child only when a parent is assured that the lack of benefit is balanced by a similar level of significant risk. "The principle of beneficence establishes both parental and societal responsibility to protect a child by assuring that the child is not placed at a disadvantage by being enrolled in research" (Nelson, p. 164).

Parents are by definition in a position of weakness when considering such a decision. They have neither the scientific background of the investigator proposing the research nor the ethical/regulatory background of the human subject review committee that approves the study. However, the parents are the third leg of the protective triad in the enrollment process, a role they can fulfill only if they understand not only the process of the study – what will be done – but also what are the future implications for the family when the data are collected and analyzed (Miller & Weijer, 2005). For instance, one multisite study of the understanding of parents who enroll their children in leukemia research trials found that 50% of the 137 parents observed did not understand the concept of randomization (Kodish et al., 2004). This was despite rather intensive educational sessions during the enrollment process.

Prior to the enrollment of any child in a research trial, permission is solicited and obtained in almost all cases from his or her parents. In research that is considered therapeutic, it is accepted that parental permission is necessary in most cases prior to going forth with research and that parental dissent to a proposed trial disqualifies the child from participation (Kodish, 2005). Such a position supporting the role of the parent as the proper decision maker in this situation derives from the traditional belief that parents are the best judges of their children's interests and that they should be given much leeway in how they raise their children within the framework of their cultural and moral beliefs about family life. With the few exceptions being situations when parents truly act in ways that are not in the best interests of their children, the legal trends are to respect parents' judgments in matters of medical care, including research participation (Collogan & Fleischman, 2005).

Views of parents about allowing their children to participate in research. There have been several studies that examined the reasons that parents reported for enrolling their children in therapeutic drug studies. Tait and associates report on decisions of families originally enrolled in anesthesia studies (Tait, Voepel-Lewis, & Malviya, 2003a,b,c, 2004). Consenting parents were more likely than non-consenting parents to

- have more confidence in their decision than non-consenters;
- trust the investigators;
- believe they understood the consent form fully;
- have confidence in the investigators' abilities;

- feel comfortable in the research environment; and
- have positive feelings about the research environment.

Caldwell and colleagues (2003) conducted focus groups to determine why 33 parents enrolled their inpatient children in studies at an Australian children's hospital. Common themes among parents in this study were that parents would like to know their doctor's recommendations about participating in the trial and desired more discussion of the details of participation.

In another study, a 14-item questionnaire was given to 44 parents who had already enrolled their children in asthma drug trials. The two strongest factors that led to enrollment in this group were the opportunity to get access to new drugs, and knowledge about the disease. The least contributory factors were incentives or social pressures to enroll their children, though low-income parents significantly linked access to free medications as a reason to enroll their children (Rothmier, Lasley, & Shapiro, 2003).

Broome has put forth a review of literature that summarizes the factors that affect parental enrollment of their children as informational, illness context, diagnosis and treatment recommendations, and child and family individual characteristics (Broome, Richards, & Hall, 2001). In a related study, she interviewed 34 chronically ill children and adolescents about how they conceptualized the issues about their enrollment in studies and focused her findings on the effect of the relationships the children had with parents and investigators on the decision to participate. In this group, the children and adolescents both felt that adults would support them in their decisions to participate or not (Broome & Richards, 2003).

Such findings may be particularly pertinent for genetic research, for commentators have noted that there may be subtle risks that currently go unrecognized in some forms of genetics research with children (Patenaude, 1996). A group of investigators who offered therapeutic gene transfer technology under the research process to children with a fatal genetic neurodegenerative illness described the complexity of the enrollment decisions faced by the parents. The study used a single case description of an enrollment process that exhaustively discussed issues such as the difference between research and proven treatments, why one child was offered the trial and another might not be, and the differences between the child's health caretaker and the researchers. The authors recommended a process of monitoring the interpretation of information during gene therapy trial permission procedures with parents to make the enrollment decision most meaningful (Arkin et al., 2005). The appearance of this discussion in the literature and the fact that it was entirely a theory-based bioethical discussion underscores the need to collect data to determine whether such concerns are based on true parental knowledge needs.

Parents who are approached about enrolling their child in a genetics research trial have several issues to consider. When investigators assure confidentiality of genetic results, does that mean the parent can be confident that all details of enrollment, including records of any related

procedures billed to insurance companies, will stay private and unobtainable in the future? Will children in population-based research be at risk for discrimination by published results that have public health implications and thereby can be promulgated in ways that cannot protect broad evidence of participation (Campbell & Ross, 2003), such as when a gene associated with behavioral problems is identified? And should investigators and regulators consider whether a health-related genetic finding in a child subject needs to be shared beyond the nuclear family or even shared at all (Bookman et al., 2006)? It is necessary to begin assessing what information parents will need to make their decision making during the permission process more meaningful so that such questions can be addressed (Patenaude, 2005).

CURRENT STATE OF PEDIATRIC GENETIC TESTING UNDER RESEARCH INITIATIVES

Molecular genetic testing for specific genetic disorders is relatively new. Only within the past two decades has such testing moved beyond simple karyotyping for disorders of the chromosomes to directed testing for specific genes that are diagnostic for or linked with health disorders. While single-gene diseases such as cystic fibrosis or neurofibromatosis 2 can have their respective recessive or dominant genes identified in specific patients, relatively few people are diagnosed purely through a genetic test. Instead, such testing usually occurs after a risk assessment of a specific illness that has occurred within an individual child's family or because of emergence of new symptoms that suggest a hereditary cause that is linked with a diagnostic genetic test. Indeed, most genetics health professionals believe that most future genetic diagnoses will show that the etiology is *multifactorial* or a combination of genetic and external risk factors, such as when a person genetically predisposed to skin cancer undergoes enough sun exposure to trigger the growth of malignant tumors.

Molecular genetic testing of children takes place in different venues. Increasingly, such tests are available through commercial laboratories for clinical use (http://www.genetests.org), but there is still a significant amount of genetic testing for clinical illness that takes place under research auspices. Additionally, genetic testing of children often occurs through enrollment in clinical studies in which genetic inquiry is not the primary goal of the study (Chang et al., 2009)

Newborn Screening

Almost all American children undergo a set of genetic tests shortly after birth, through newborn screening programs in each state and territory (http://genes-r-us.uthscsa.edu/index.htm). Individual states have different tests contained within their panels and most of the screened disorders have genetic etiologies. States considering adding new tests often do so after piloting such testing under research auspices, such as when

Wisconsin and Massachusetts studied the possibility of screening newborns for cystic fibrosis (CF). Ethical issues that arose within the original Wisconsin setting included whether parents need to be involved in the enrollment of their children and whether the use of a control group in evaluating the effectiveness of a new test for genetic illness in a population with an unknown risk ratio should be acceptable (Taylor & Wilfond, 2004). In the Massachusetts study, parents were given informational pamphlets about the study and could opt out of the study (Comeau et al., 2005)

Therefore, it is very common for children in the United States to be in involved in genetic testing, through newborn screening research protocols. With the continuing expansion of genetic screening technologies, it is not unreasonable to expect more possibilities for families with newborns to be asked to enroll their neonates in such screening studies (Jenkins, Rasmussen, Moore, & Honein, 2008). The key ethical issue in this scenario is whether the involvement of the family in the research enrollment process is thorough and voluntary.

Studies of recessive genes in children–newborn screening. Because most metabolic disorders that newborn screening reveals are recessively inherited, most initial tests only discover the presence of one disease gene (http://www.newbornscreening.info/GlossaryTerms/autosomalRecessive.html). In recessive disorders, a pair of the specific genes is necessary for the disease to be expressed. Additional laboratory studies are usually necessary to determine if the child has the illness. Therefore, many more unaffected children with one disease gene are diagnosed. There are particular ethical issues when such *carriers* are identified early in childhood.

Children who are tested early in life may lose contact with those professionals who conducted tests that revealed a positive carrier state (Fryer, 2000; Hoffmann & Wulfsberg, 1995; Lessick & Faux, 1998; Ross & Moon, 2000; Ross, Newburger, & Sanders, 2001). Such disease-free carriers have been documented as having significant knowledge deficits about the meaning of their genotype for their health (Fanos & Johnson, 1995). Additionally, a pilot study of 15 college youths who had been identified as carriers for sickle cell anemia or hemophilia at a mean age of 9 found that the subjects stated a great need for education about their health status that their parents were unable to meet (Hern, Beery, & Barry, 2006). If increasing numbers of asymptomatic children are identified as being carriers of varied genomic conditions through newborn screening research, consideration must be given to the possible harms and benefits of these tests. While asymptomatic carriers cannot receive any medical benefit from being tested, there is controversy over whether having one's genetic health data available is more beneficial or possibly harmful, as will be discussed later.

Genetic Studies in Symptomatic Children

When a child presents with a set of physical symptoms that suggest a genetic etiology, it is normal for testing for a responsible gene to be done under research auspices if such testing is not available through clinical

care. Though single-gene disorders such as CF have increasingly been identified and specific genes located for the illnesses, research continues for variations within the phenotypes possible for variations within a given illness. Therefore the initial molecular genetic test that a child undergoes to aid in diagnosis may be done within a research protocol. The questions that should be asked about this research are whether the tests will provide clinically useful data, how much of the test results will be available to the family, and if the results will be used to provide therapeutic interventions (McConkie-Rosell, Spiridigliozzi, Melvin, Dawson, & Lachiewicz, 2008).

Genetic Studies in Children with No Genetic Risk Factors

Quite probably the largest groups of children who are enrolled in research studies that collect genetic material for examination are those who participate in protocols that are examining a health issue from a biophysical or psychobehavioral perspective and that make part of the data collection the donation of a tissue specimen for genetic analysis. An example from the author's own experience as a reviewer for the Institutional Review Board (IRB) at a major academic medical center is protocols that test medication in children with behavioral problems. Consistently, such studies collect and store genetic material for examination of *single nucleotide polymorphisms* (also known as candidate genes or SNPs) that may be linked with the disorder or pharmacological response of the child. The justification is that most genetic disorders are considered to be multifactorial and that by studying clusters of subjects with similar characteristics, genetic similarities may be identified. Ethical issues worth discussing emanate from enrolling children in these studies and will be discussed later in this chapter.

ETHICAL ISSUES ABOUT GENETIC TESTING IN CHILDREN

Historically, professionals hesitated to recommend genetic testing of children if there was no direct benefit to them or an affected family member that may result from the test outcomes. Several professional associations have developed policy statements that urge caution when considering such testing in children (American College of Medical Genetics, 1995; Great Britain Advisory Committee on Genetic Testing, 1999; American Academy of Pediatrics, 2001; Clinical Genetics Society, 1994; Canadian Pediatric Society, 2003). However, there is controversy over how rigidly clinicians should adhere to these guidelines when parents approach them about having their children tested for therapeutic reasons or simply to gain knowledge about their child's genetic health (Rhodes, 2006).

A review of issues-oriented articles on the ethics of genetic testing in children reveals two common themes. The first is that children are not yet considered autonomous human beings. Testing children before they can participate in the testing/counseling process weakens this developmental

process needlessly as they may lose control over the flow of their personal medical information (Clayton, 1995). Children have privacy rights, and parental knowledge of genetic information is thought by some to compromise these rights (Quaid, Jessup, & Meslin, 2004), particularly in the area of future reproductive decision making (Borry, Fryns, Schotsmans, & Dierickx, 2006).

Second, any recommendations for genetic testing should be saved for those who will use the information for immediate medical intervention, such as when a family with documented hereditary colon cancer wishes to test their young asymptomatic children in order to spare them from unnecessary surveillance procedures or to see if an affected child would receive benefits from interventions before symptoms occur (Olsen & Zawacki, 2000).

Conversely, testing of children for diseases that have no actual or anticipated therapy provides no benefits to them directly. While parents may state that the potential benefit will accrue indirectly by allowing the parents to have information useful in managing future genomic health issues, it is unclear how such knowledge will be used. Ross notes that predictive newborn screening for type 1 diabetes has been offered in at least one state and warns that unless such efforts are accompanied by preventive measures for those who screen positive, then harms may outweigh benefits. Her conclusions are that if the population tested is not at high risk for the illness then the process of screening may increase psychosocial stress in families, while if there is no intervention for those children who test positive, then such knowledge should be kept confidential to avoid parental anxiety over the increased risk for their child (Ross, 2005).

Commentators have noted several other concerns about early genetic testing in children. Do children have a negative right to not know their genetic status (Elger & Harding, 2000)? From an ethical perspective, this refers to the loss of future autonomy because of the inability to decide for oneself whether to be tested for a given gene (Kurtz, 1998) and becomes an issue generally if there is no likelihood of clinical benefit resulting from such a test. It is hard to claim, though, that an ethical harm occurs when children's decisions are restricted and parental choices in the present negatively affect the child's future. Such occurrences are part of family life: Parents would be paralyzed in their child-rearing if every possible outcome of a parental judgment required a determination of all possible outcomes.

Because of the changing developmental stages of individual children, special protections are extended to minors recruited into any research. Federal law mandates such protections that include provisions for restricting children from enrolling in nontherapeutic studies that may pose more than minimal risk. These protections are maintained primarily through the enrollment process that mandates parental permission for enrollment in most studies as well as the assent of the involved child (Broome, 1999). Thus children are regarded as a vulnerable population for which specific protections must be extended when they are recruited for enrollment into research.

Research into Risks Involved in Genetic Assessment in Children

Risks of participating in genetic research are related to the type of trial in which a child is enrolled. In the type of genetic studies that collect specific disease-related genes for a suspected genetic illness within a family, the risks center mostly on how the personal genetic knowledge that the child and/or family receive from the study will be used and possibly shared with third parties. If the nature of such genetic research is not properly understood, as in a sample of 130 adults who underwent clinical genetic testing reported (Wendler, Prasad, & Wilfond, 2002), the misunderstanding about the information may cause the family to fail to access any possible benefits from the information that results from those trials and any that result from the trials in which their child was enrolled. If the findings reveal a genetic diagnosis that causes some psychosocial stress but does not point to any medical interventions, then the harm may not be balanced by concomitant benefit, as research on minors requires (Ross, 2001, 2003a). In other genetic studies seeking candidate genes, the risk would emanate from any loss of confidentiality about one's genetic makeup (Cooper, Nelson, & Ross, 2004), as well as potential misinformation regarding the child's present or future health, and subsequent loss of personal, family, or societal benefits.

Concerns about the effects on children after receiving information about genetic assessment have focused on such entities as depression, anxiety, fear, and other related emotional reactions to the news that a genetic illness has been discovered within a family and that they are at risk. Whether the genetic assessment performed is *presymptomatic* (which indicates a positive diagnosis), such as the test for familial adenomatous polyposis (FAP), or *predispositional* (which indicates a higher likelihood of developing the illness), as are the results from the breast cancer genetic mutations (*BRCA*1/2), the small studies that have been done fail to show significant harms occurring, within the time frame of the study, because of the testing. These studies have covered a fairly broad grouping of disease mutations. Twenty children aged 11–17 who lived in families with hereditary breast cancer were surveyed about feelings of stress and anxiety and completed standardized measures of depression. The results did not reveal any unusual cancer worries or increased psychological adjustment problems, though the small size of these samples preclude any firm conclusions being drawn at this stage (Tercyak et al., 2001a; b; Tercyak, Peshkin, DeMarco, Brogan, & Lerman, 2002; Tercyak, Peshkin, Streisand, & Lerman, 2001c). Two studies followed children after being tested for the adenomatous polyposis coli gene mutation (*APC*) that is linked with FAP. In the first, 48 children aged 5–17 years were followed for a mean of 38 months. Three assessments at 3, 12, and 23–55 months included standardized measures of pediatric depression, anxiety, and behavior. In both the groups of 22 children who were positive and 26 children who tested negative, few long-term untoward psychological effects were found in these children who were coping with the knowledge of their own test results and in 21 cases, knowledge of a sibling's positive test for the *APC* gene (Codori

et al., 2003). In the other study of 60 children, aged 10–16 years, tested for *APC*, no increases in psychological stress were found in the group who were either positive or negative (Michie, Bobrow, & Marteau, 2001). In another study of 46 families that tested their daughters aged 5–17 for either the Duchenne muscular dystrophy or the hemophilia A gene mutations, about three quarters of the parents notified their children of their status as either an unaffected carrier or not a carrier (Jarvinen, Lehesjoki, Lindlof, Uutela, & Kaariainen, 2000b). This group of parents and a group of 25 adult siblings tested for carrier status as children for a lysosomal storage disease were followed for 10–24 years after testing and did not report feeling any harm from being tested (Jarvinen et al., 2000a).

There may be some long-range effects of being tested as a child for a genetic illness and finding that one is a carrier of a recessive mutation. Fifty-four adults at risk to be carriers of cystic fibrosis misinterpreted their carrier status as having health implications that were inaccurate, such as them having no personal risk for developing the illness or that being a carrier predisposed them to developing respiratory illnesses. Many of these siblings expressed guilt over being a healthy child with an ill sibling, but this was not related to being tested (Fanos & Johnson, 1995, 1995b). Another group of 27 unaffected adults who were tested as children to analyze the pattern of mutation for ataxia telangiectasia in their siblings reported generalized anxiety about the procedure and the meaning of the test results. A lack of genetic counseling seems to have contributed to this group's feelings about the testing experience (Fanos & Gatti, 1999). However, a systemic review of 30 studies that measured effects of pediatric genetic testing found that there is little evidence that significant long-term psychological harms occur secondary to receiving genomic information from being tested as a child (Heshka, Palleschi, Howley, Wilson, & Wells, 2008).

Some experts have argued that parents should have more latitude to have their at-risk children tested at the parents' discretion. Grosfeld et al. (1997) noted that the fluid aspect of possible therapies for some genetic cancers (including, presumably, experimental therapies) may make early testing and preparation advisable. Cohen (1998) and Pelias (2006) rejected the argument that parents should be dissuaded from early testing based on ethical notions of child autonomy. They noted that not only do parents traditionally assume great leeway in making decisions that will affect future lifestyles of their children, but that parents, not professional counselors, are the best equipped to decide how well their progeny will react and cope with information about their genetic makeup. Rhodes (2006) has taken this argument a step further by declaring that there is a positive benefit to harm ratio in predictive genetic testing for adult-onset diseases and urges caretakers to recommend such testing to parents. Duncan and Delatycki (2006) agree, noting that 15 years of discussions about the issue have failed to produce any empirical evidence of harms to children from predictive testing and that it would be more useful to develop guidelines that facilitate such testing and provide for follow-up of those families who avail themselves of such opportunities in order to study the effects systematically.

Factors Affecting Parental Enrollment Decisions

Several factors appear to affect parental decision making about enrolling their children in research studies. The first factor is recruitment sources. Children are recruited to trials primarily through parents and by the health-care professionals who counsel them about enrollment. Barriers to enrollment that professionals have noted as they consider whether to refer their patients into research trials include their own lack of knowledge about trials and concerns about referring patients at all into research trials (Caldwell, Butow, & Craig, 2002).

Another factor affecting enrollment includes methodological issues. Many types of research trials have been open to children, including observational research of development, behavioral research, and other types of research that is considered low risk. Conversely, children have traditionally been recruited into "therapeutic" trials when they were ill. Examples include chronically ill children in oncology trials. Such trials have carried higher levels of risk but have been considered permissible under federal regulations and by IRBs because of the possible benefits that the ill subjects might access (Glantz, 1994). Current initiatives to increase pediatric research will necessitate enrolling larger numbers of healthy and ill children into trials, including those protocols that are testing interventions that may pose no benefit to the enrolled children, such as testing of medications for occasional use in healthy children, such as analgesics. Traditionally, there has been a hesitancy to include children in the latter types of trials (Ross, 2003a).

The developmental level of the child is a third factor that must also be considered. The literature about children in such clinical trials is dominated by discussions that reflect research findings about the levels of decision-making competency of children of varied age and developmental levels to participate in the enrollment process (Broome, 1999). To summarize the general finding of such studies, children have high enough levels of comprehension about participating in research as they attain basic cognitive skills, such as reading and writing, which occur at about age 7, to participate rudimentarily in the enrollment or consent/assent process. As children grow cognitively, their capacity to understand what will happen in a research study increases as they approach early adolescence, around ages 11–12 years. By middle adolescence, or by high school, teens have a similar appreciation of present and future effects of participating in research such that their decisions are similar to those of adults (Miller, Drotar, & Kodish, 2004). Overall, studies that elicit children's understanding of research enrollment issues are rather limited in scope as well as breadth.

Parental factors have been the most extensively studied with regard to parental decision making and enrollment of their minor age children in research. Federal regulations that guide investigators and human subjects reviewers detail the involvement of parents in the enrollment process of trials using a framework in which the higher the risk in the trial, the higher the involvement of one or both parents in the permission process (Miller & Nelson, 2006).

Genetic Testing of Children

Decision making in families about sharing genetic information is quite complex, particularly when such sharing involves discussion with children (Geller, Tambor, Bernhardt, Fraser, & Wissow, 2003). It seems to focus on the value placed on possible information that might be attained and shared, personal values about the best interests of their children, what information needs to be protected, and the developmental ability of a given child to receive and use such information (Hamann et al., 2000). Researchers who enroll children in genetic studies will have to take such factors into consideration as they construct assent/consent forms for genetic studies.

Familial Sharing of Genetic Information

It is reasonable to believe that parental attitudes toward genetic testing in general and genetic testing of their children specifically will impact their willingness to consider research studies involving genetic analysis of their own children. While there is scant literature about parental attitudes toward genetic testing, results of studies of adults that focused on genetic testing of themselves for familial risk for hereditary breast and ovarian cancer indicate that parents see genetic testing as a family issue. In one study of 192 parents with hereditary breast and ovarian cancer (HBOC) in the family, 78% noted that the most important rationale for seeking testing for themselves was to obtain genetic information for their children, while another 18% said it was somewhat important in their decision to test themselves (Lerman et al., 1996). Similarly, in a study of 16 families that elicited beliefs about HBOC mutational testing from mothers and daughters aged 10–17 years, the mothers believed that having the genetic information about a HBOC gene will lead to a cure, better surveillance, or screening, and the interviewed daughters tended to agree with their mothers (Geller et al., 2003).

However, in survey of 104 parents in a HBOC surveillance program, only 18 would test their own children while a larger percentage, 25%, would support such testing as a policy (Hamann et al., 2000). This is in contrast to some surveys of professionals who report rates of up to 50% who are willing to test children for genetic disorders when given conjured scenarios (Harman, 2003; Rosen, 2002). These attitudes were affirmed in a description of international practices of genetic testing where 301 respondents reported 22 cases of testing of immature minors for late-onset disorders where no therapy was available (Duncan, Savulescu, Gillam, Williamson, & Delatycki, 2005). The professional respondents in these surveys appear to believe that individual parental requests for information deserve preference to adherence with professional guidelines.

DISCUSSION

The core concept of being a research subject is that no matter what the nature of the research project eliciting one's participation, there is

some level of altruism. Whether it is a subject or a surrogate, the decision whether to enroll or not always requires an assessment of how much acceptable risk can be assumed, even if the desire is to donate heavily to science and the good of humanity. As seen, the level of voluntary altruism is significantly limited when children are the possible subjects (Simon, Eder, Kodish, & Siminoff, 2006).

Genetic research further muddies the ethical waters. The current nature of genetic research is such that almost all of such research is a request for information. But this information is immortal, it is individual, it is shared, and most importantly, it is malleable. Genetic information has always been subject to value judgments, within families and greater society. Also, the probabilistic nature of genetic information means that receiving it is similar to being given the gift of a set of puzzle pieces: Sometimes you will be certain that the box contains 100% of the puzzle, while at other times, being tested may only provide several pieces that are not interlocking and may not even match in color. Even for some of the most accepted predispositional tests, such as the *BRCA* genes, the puzzle may predict a picture of high likelihood of illness but how one wants to view the missing 25–50% of the picture truly lies within one's view of the world, medical technology, and the counseling one receives.

So how should we evaluate risk of harms and possible benefits in pediatric genetic research? Hoedemaekers (1998) has advised being very cautious in considering the risk involved in genetic testing. The information derived from such testing is often imprecise and incomplete. When one factors into this difficult calculus the point that it is unpredictable how a given family member will interpret results, determining whether a child will be harmed by being tested is probably impossible. From an issue of privacy, the future of genetic discrimination is unpredictable. Despite the fact that the Genetic Information Nondiscrimination Law of 2008 has been passed into law and signed, its long-term effects on reducing discrimination in employment and health insurance based on genomic information cannot be predicted until the rules promulgated for its enforcement are tested (http://www.dol.gov/federalregister/HtmlDisplay.aspx?DocId=21604&AgencyId=8&DocumentType=1).

We are reaching a critical point in the ethics of pediatric genetic testing in research. There has been discussion within the genetics community about the moral duties owed from researchers to their subjects, particularly to those children with no genetic risk factors who are solicited for their genetic material to look for varied genes possibly associated with diseases. Questions arise such as whether to disclose any results to the participants, individually or in the aggregate (Ravitsky & Wilfond, 2006). If the research on deposited data suggests analysis in directions not initially anticipated, should the family be approached to sign updated enrollment and assent forms (http://www.hhs.gov/ohrp/informconsfaq.html#q11)? Will child subjects later feel stigmatized if genetic material they donate links them or their ethnic group with undesirable characteristics, such as behavioral issues (Cooper et al., 2004)

So far, many of the ethical issues have been essentially shunted aside because of the widespread practice of researchers, abetted by IRBs, to collect such material and immediately anonymize it and analyze it only in the aggregate (Ravitsky & Wilfond, 2006). This is the practice in most studies that collect genetic material. The presumption is that the greatest threat to the subject is being linked with their genetic data, presumably because of possibility that it could be used to discriminate against them. But this argument relies on a belief that genetic knowledge has little or no beneficial value to a subject. And that assumption is bolstered by the fact that many researchers consider such genetic material as subsidiary to the main goals of their protocols. Such genetic material is referred to in assent/consent forms as being something that will be stored and looked at in the future, almost as an afterthought. Investigators have to justify that they have enough scientific rationale that such material may have important implications as more is discovered about genes and their impact on health. So future significance may be the key to today's collection of genetic material from minors (Burke & Diekema, 2006).

Looking toward the future is not unknown in clinical research, which by definition studies the effects of phenomena in populations, not individuals. But it is becoming more common for researchers to be held responsible for examining whether the analysis of their data has immediate health implications for individual research participants. An example is the frequent use of magnetic resonance imaging (MRI) to visualize anatomical structures while collecting varied data about clinical phenomenon. Researchers who use this method will say that they are only interested in isolated structures and functions, but IRBs increasingly are insisting that individual MRI findings be viewed by a medical specialist who can analyze the findings and note if any gross abnormalities are evident. If so, the involved subject is notified, given a record of the MRI, and instructed to obtain further consultation about the findings. Furthermore, investigators who are studying clinical findings over a long term in a population that shares a health problem, such as cardiac disease, are being directed to develop some system of notification, such as an annual newsletter (Ormand, 2006), which gives subjects a report of recent findings of the study. They can then discuss such findings with their own provider, to see if they might need further workup of their individual illness. This is a significant change from traditional practices, where researchers who were not directly involved with a given patient-subject's care would assume that the patient's provider would be reading the scientific literature to keep up with new findings.

So future significance may be the key to today's collection of genetic material from minors. The key issue is whether to provide genetic test results to participants. One argument for divulging genetic results to participants recommends that the higher the clinical utility of a test result, the more responsibility the investigator has to share the data, particularly if the research has enrolled the subject because of a clinical relationship with him/her (Ravitsky & Wilfond, 2006). Supporters of this position certainly look toward enhancing the benefits that subject may take from participation in the study. However, it has been pointed out that such

policy also further emphasizes the autonomy of the subject, for it supports the argument that individuals best know what is most meaningful to them (Lavieri & Garner, 2006). For instance, consider the adolescent who is recruited as a control subject into a trial that is seeking SNPs for migraine headaches and after the trial, her family is notified that the trial found several SNPs that were associated with migraines and that her genotype contains one of the SNPs. If the proper genetic counseling is available, this individual could take into account that she has never had symptoms of migraines, realize that perhaps she has some level of elevated risk for future development of such symptoms, and that perhaps she now has an extra piece of information about her health history that may aid her (or a family member) in the future. If she does not have the information, some would argue that the ethical evaluation is neutral; she has received neither benefit nor harm. Questions such as this regarding genetic research involving children in nontherapeutic settings will certainly continue to be discussed in the future.

Arguments against the sharing of information include that it may be too hard logistically for investigators in large trials to provide individuals their results (Fernandez & Weijer, 2006), that it is very difficult to present genetic findings in a meaningful way to individuals (Klitzman, 2006), and that this practice would blur the distinction between research and clinical care (Fryer-Edwards & Fullerton, 2006). Probably the case against providing individual results that warrant the most attention is that based on the reality that there are genes that are *pleiotropic* (Jorde, Carey, Bamshad, & White, 2003). This aspect of some genes means that they have multiple effects. Therefore, when one tests for the gene, you may find that someone has the likelihood of several physical manifestations.

A dramatic example of this in predispositional genes is the *APOE* gene, which is linked with some cardiac conditions and with some manifestations of Alzheimer disease (http://www.labtestsonline.org/understanding/analytes/apoe/test.html). If one enters into a trial examining the effect of a medication on cardiac function and the investigator is collecting *APOE* SNPs from affected and control subjects, the edict that results be furnished to all subjects may mean that people who thought they were enrolled in cardiac research are being given information that they are at risk for a degenerative neurological disorder. To minimize the possible harm of this research finding, the consent process would have to be very detailed and probably would draw attention from other aspects of the protocol that need explaining. A further problem would occur when the protocol has a long time from sampling to analysis, resulting in an unavailability of data for many years. Would possible benefits be diluted because a window of time may have closed because subjects with linked SNPs for a disease were unable to act to ameliorate symptoms or illness development, such as type 2 diabetes?

For children, the issue of temporality is crucial in the ethical analysis of genetic research. If one considers the transfer of information for beneficial use the key issue to be addressed, then children have arguably a larger stake in having access to their genetic information than adults. If a child in the early part of their life is going to donate genetic

material for examination that eventually proves to have significant health implications, then the developing child has an individual claim on having access to such information if it may allow him or her to optimize health choices. This claim to benefit is not just an individual claim but can be extended to the community as well. If the individual participates in genetics research that is low risk, such as simple donation of blood that is examined for genetic influences on childhood obesity, then the community also profits from programs designed to counteract environmental and genetic predispositions that may influence the amount of children who grow up overweight.

Timely sharing of genetic research results also promotes the autonomy of the child, a developmental concept that many pediatric specialists will see as necessary for all involved in the care of a child. This is an ongoing task that researchers can assist in by assessing what information may be produced within their genetics studies. Specific instances include when unaffected carriers are identified through studies (Hoff, Hoyt, Therrell, & Ayoob, 2006). From a parent's perspective, a child will be most prepared for such information as they become more sophisticated cognitively and can use the information, such as for reproductive planning. Additionally, children who are identified as at high risk for adult-onset illnesses should be counseled in detail as they get closer to the age where interventions are appropriate (Bradbury et al., 2007).

A further concern can arise when an investigator is doing genetic research on family clusters and non-symptomatic children are enrolled to examine family patterns of known disease. While this type of research can be considered possibly beneficial because of the knowledge gained for the individuals, this is only possible if such results are available. It is likely that information that accrues will be most beneficial to affected individuals and to the family as a whole, while the child may not even be consulted about participating. Researchers should be very insistent that the assent process is honored and meaningful. Quite often when adults are making family decisions, the individual's interests can get lost.

Traditional research ethics does not address this shifting focus well. The National Commission's deliberations and the subsequent guidelines of the Common Rule place the lens of analysis on the individual, hence the preponderance of attention on the principle of autonomy. But promotion of autonomy derives chiefly from the desire to respect the personhood of the human subject and is manifested in promoting informed decision making (Evans, 2000). This is problematic in the study of the ethical treatment of the child and family for several reasons. First, autonomy in minor children is a goal, not a given state. They have few legal rights and the focal point of such rights is protection. Additionally, while parents have the prime role in protecting their children, few would argue that a child is best nurtured by simply protecting her from all threats. Instead, parents have the challenge of allowing their children to face increasingly complex decisions as they mature and to allow their children to assume risks that prepare them for the possible harms and failures that life in the world holds (Geller, 2005). So simply adhering to an ethic that has a cardinal principle of protection does not seem to serve either families or even researchers, who

also are striving to maximize the health and well-being of children in the aggregate.

Instead, there is an increasing amount of attention being paid to ethical frameworks that look at the personhood of the individual as having worth when viewed against the background of their role of the group. Such ethical concepts that emerge from these frameworks include the value of *interdependence* between individuals being as important as independence, and the goal of relationships between individuals being more important because the *mutuality* of goals can spur actions that increase the value of working within a relationship, instead of simply promoting autonomy (Noddings, 2003)

Such an ethic is quite meaningful when applied to families (Nelson & Nelson, 1995) and is particularly significant when examining decisions regarding genomic health (McConkie-Rosell & Spiridigliozzi, 2004). Whereas traditional ethics will isolate the child's participation in research as separate from the family, a family ethic will take into consideration issues such as family context, i.e., size, parental values, traditions, and goals of the family unit that transcend the simple protection of the child. This framework is extremely pragmatic, for it coheres to the actions of families as they work. On a daily basis, parents make mundane decisions about how much money to spend on clothes and how to plan meals that take into account the best interests of the group. This framework increases in complexity as family resources are balanced to enable children to make reasonable choices about things such as college choice.

The data tell us that parents use similar decision-making processes when facing decisions about genetic testing within the family. Parents discuss how they have personal genetic testing so that they can provide information. In one study, they reported that they had their young child tested for adult-onset genetic illness neurofibromatosis 2 well before any therapeutic action could be taken so that they could plan for the future (Twomey, Bove, & Cassidy, 2008). So it seems reasonable that most parents have the capability to make decisions within the context of the best interests of their families when it comes to genetic testing.

Drawbacks of employing a family ethic to pediatric genetic testing research mostly lie within the fact that current guidelines do not allow for consideration of factors other than adequate protection and enrollment procedures. For parents to make meaningful enrollment decisions, they need to be assured that the genetic research process will allow them to access results in not only ways that are understandable but ways to make such information relevant within the individual family.

There is an understandable hesitation among researchers to commit to providing research results to families. Beyond the hesitation most investigators have to being forced to release data that they have not fully analyzed, there is the very real issue that few researchers employ genetic counselors as part of their teams. This latter point is a key issue in genomic health in general. Adequate genetic counseling is in chronic shortage in most health settings (Weil, 2000). Not only do few physicians and nurses receive specialized training in genetics,

there are only 33 schools of genetic counseling in the United States (http://www.abgc.net/english/view.asp?x=1643), which prepare practitioners at the graduate level. Currently, the resource of genetic counseling is in a severe shortage.

This specifically impacts the ability of researchers to share their results with families. Genetic counselors deal with risk assessment. They provide families with understandable information that helps them to comprehend the choices that genetic data present them about their children. Not only are immediate choices impacted by a lack of counseling, but, as children grow, their genetic status as carriers of disease genes will impact their reproductive status. Without long-term follow-up, their ability to derive benefit from the donation of genetic material diminishes and eventually becomes virtually meaningless. Therefore, before we continue our sanctioning of continued genetic testing in research, consensus should be reached within the clinical and research communities about how to develop ongoing genetic counseling resources.

CONCLUSION

The current bioethical framework that emphasizes protections for children who participate in genetic research is lacking because it focuses on the risk of harms that are difficult to calculate. The current practice of researchers to deal with the issue of protection by simply declaring the collected data as anonymous and claiming that this practice of confidentiality meets the requirements to protect subjects fails to address the realistic claims that families make that having access to such data is within their children's best interests. A family ethic that recognizes the ability of parents to make decisions to allow enrollment of their minor child to donate genetic material to researchers that balance risks and benefits will be meaningful only if adequate resources are accessible that provide counseling in the short and long term to families about the meaning of the genetic tests to the family's and the child's health. Genetic researchers and health-care policy makers should work together to provide such resources, and research regulators should recognize the need to include such resources as necessary parts of the contact between researchers and their pediatric subjects.

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20

Ethical, Legal and Social Issues in the Genetic Testing of Minors

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INTRODUCTION

Since the availability of testing for hereditary diseases, genetic testing of minors has stirred controversy as regards the ethical implications of the tests. The fear that genetic testing of children could have adverse social, emotional, psychosocial and educational consequences in childhood or later life has motivated a cautious approach. Since the 1980s, several professional organizations and appointed commissions have issued guidelines. In 1983, the report on *Screening and Counseling for Genetic Conditions* of the President's Commission included a discussion about ethical issues of newborn and carrier testing (President's Commission, 1983). The Institute of Medicine (1994) examined the social, legal and ethical implications of genetic testing in 1994 and considered explicitly testing of minors (p. 297). During the same year, a report from the Working Party of the Clinical Genetics Society (UK) was published on "the genetic testing of children" (Clarke, 1994) and 1 year later the American Society of Human Genetics, together with the American College of Medical Genetics, expressed their views concerning the *points to consider: ethical, legal and psychosocial implications of genetic testing in children and adolescents* (American Society of Human Genetics [ASHG]/American College of Medical Genetics [ACMG], 1995). In 1998, the Working Group on Genetic Testing for the National Human Genome Research Institute followed with its final report on *Promoting Safe and Effective Genetic Testing in the United States* which contains chapters on newborn screening, carrier testing and presymptomatic testing of children (Holtzman & Watson, 1998). Most recently, the American Academy of Pediatrics issued a policy statement in

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2001 on *Ethical Issues with Genetic Testing in Pediatrics* (Committee on Bioethics et al., 2001) and reaffirmed it in 2005.

In addition to general ethical guidelines concerning genetic testing of children, a number of guidelines on genetic testing for specific diseases refer to the ethical problems of gene tests of minors with respect to this limited number of diseases. An important example of such recommendations that were among the first to be published were guidelines concerning predictive testing for Huntington's disease from the World Federation of Neurology Research Group on Huntington's Chorea (1994) and from the European Community Huntington's Disease Collaborative Study Group (1993). Both stated clearly that genetic testing for Huntington's disease should not be carried out in individuals under the age of 18.

Recommendations concerning testing of children for Huntington's disease have remained the same until today. Interestingly, the same is true for the content of general guidelines. All major positions expressed in guidelines, as well as the standards by which the acceptability of genetic testing of minors may be judged, did not change over the past 25 years.

In summary, guidelines agree that genetic testing of children should be used in a cautious and restricted manner. It is appropriate in two situations. The first is the testing of a symptomatic child if the tests are likely to help establish a diagnosis and/or a prognosis and to avoid further invasive diagnostic tests. The second is predictive genetic testing in healthy children where onset of the condition regularly occurs in childhood and "there are useful medical interventions that can be offered (for example, diet, medication, surveillance for complications)" (Clarke, 1994). In these cases, testing should be done as late as possible, in general not before the earliest age of the onset of the disease or the earliest moment when prevention or treatment need to start (Kodish, 1999). In all other cases, where no such medical benefit is expected during childhood, testing should be postponed until the child reaches the age of majority.[1] This means that predictive testing for an adult-onset disorder should not be carried out in minors; nor should carrier testing if the aim of the gene test is restricted to promoting the child's future reproductive choices and no direct benefit is expected from testing under the age of 18. Exceptions were mentioned for some situations, especially where the context implies a potential benefit to other family members. In such cases, arguments against testing need to be more finely balanced (Clarke, 1994; Hall, 2007), as will be shown below.

The existing guidelines are merely advisory and not legally binding. The professional organizations who issued the guidelines were aware that the published recommendations do not necessarily reflect the opinion of

[1]The guidelines that have been published so far do not contain a category of "adult-onset disease where childhood intervention could be useful". For example, some people think that participating in sports in childhood might be protective against breast cancer later on. This type of category could be justified once the medical evidence is sufficiently clear.

all of their members. Indeed, from the very beginning, surveys showed that the willingness to test children varied widely among different professionals. Geneticists are in general more reluctant to test children than are paediatricians whose opinions might again conflict with those of parent or patient associations (Dalby, 1995; Demmer, O'Neill, Roberts, & Clay, 2000; Michie & Marteau, 1995; Paul, 2008). Substantial minorities would allow for genetic testing of minors for adult-onset diseases as well as for carrier testing of diseases that does not have any medical benefit in childhood (Borry, Goffin, Nys, & Dierickx, 2007, 2008). It is not always clear whether this variance is due to a lack of knowledge about existing guidelines (Demmer et al., 2000) or to genuine disagreement with the published guidelines. Recent studies seem to indicate that compared to 25 years ago, clinicians nowadays have become more restrictive concerning testing and more supportive of the cautious approach expressed in the guidelines. Cultural and geographical variations notwithstanding, they favour delaying tests wherever possible as this permits preserving confidentiality and retaining a child's autonomous choice (Borry et al., 2008; Hall, 2007).

Ethical, legal and social issues in genetic testing of children are strongly interrelated. Hence, when discussing ethical decision making, we will inevitably have to refer at some point to legal frameworks and to social environments in which these decisions have to be made. In the following, we will first discuss the ethical standards that help to decide whether and under which circumstances genetic testing of children can be justified or not. Second, we show how these standards apply to different types of testing, starting with ethical problems in three controversial types of testing, beginning with the least controversial to the most controversial: newborn screening, carrier testing[2] and screening, as well as testing for adult-onset diseases. Screening (of newborns or of carriers) will be discussed as a separate issue because testing is not limited to individual families at risk but extended to the entire population, therefore adding ethical considerations about public health benefits. Carrier testing and predictive testing of minors for adult-onset diseases are chosen because both raise particularly difficult ethical, legal and social questions that warrant a thorough discussion about ethical standards. In addition we will consider persisting ethical and social problems of two types of testing that are at least partly permitted according to existing recommendations. The first example is presymptomatic testing of children with diseases for which prevention and treatment in childhood is available. This type of testing is the least controversial. Significantly fewer guidelines condone the second example which is the testing for diseases with childhood onset where no treatment or prevention exists (Borry, Stultiens, Nys, Cassiman, & Dierickx, 2006).

[2]Carrier testing in this text will be used to refer predominantly to testing of heterozygous individuals who carry a recessive gene or a balanced chromosomal rearrangement where carriers themselves are not affected but could transmit the mutation to their children and have affected offspring under certain conditions (for example if both parents are carriers of the recessive gene).

For each type of testing, we will briefly describe the range of existing arguments expressed by different stakeholders and comment on the way disagreement should be dealt with in an ethically acceptable way in this context. Finally, we will discuss further research and developments, in particular what is needed to advance ethically valid decision making in the future.

ETHICAL STANDARDS FOR GENETIC TESTING

Children and Adults

The ethical standards used to judge the acceptability of genetic testing do not principally differ from those used to evaluate other diagnostic procedures or interventions in medicine. Decisions can become more complex because test results not only imply the confirmation of a genetic disease or predisposition in one individual but can have implications for family members who might gain information about their own genetic risk depending on their blood relative's test result.

The main ethical principles used to judge medical interventions including genetic testing have been summarized 25 years ago by the President's Commission (1983): respect for autonomy and privacy (including confidentiality), beneficence (including the prevention of harm) and justice (including equity and fairness). In addition, for screening programs, a few other principles need to be added which should guide public policy: cost efficiency (or economy) and public participation (through democratic political institutions). Ethical problems concerning the genetic testing of adults are solved mostly by reference to the principle of autonomy. Indeed, guidelines on genetic testing for diseases where the benefit–harm ratio of the tests is controversial emphasize the importance of informed consent. After thoroughly informing the adult about potential risks and benefits of the test, autonomy is the overriding principle and the choice for testing is left to the competent individual. When children are tested, however, the reference to the principle of autonomy does not solve the dilemma but leads to conflicting positions. It can be used to claim a greater right for older children to decide for themselves, especially in the case of mature adolescents who fulfil the legal and ethical criteria for competency. Others refer to the importance of autonomy arguing against testing of children in order to preserve a child's possibility to decide on his/her own once he/she has become an adult. Medical decision making on behalf of others one wants to protect, such as children, does not escape the difficult evaluation of what is good and bad, a typical and almost insolvable debate in modern pluralistic societies. In the worst case, caregivers or the state might feel obligated to impose the best interest standard defined by the social, cultural and medical norms of a given society and to restrict the right of parents to define themselves the best interest of their child.

Best interest standards (Kopelman, 2007) refer almost always to benefits and harms and are evaluated on the basis of the existing evidence. Decision based on benefits and harms in genetic testing of children is

Table 1. Potential Benefits of Genetic Testing of Children

Medical (prevention, treatment)
Psychological (child will feel empowered; uncertainty is relieved; child has the time to adapt)
Social (if negative test results, i.e. absence of disease: discrimination and stigmatization can be avoided; independent from the test results: the future can be better planned)
Autonomy-related benefits (if older children are given the possibility to decide for themselves, they have a feeling of control that has positive consequences on their self-esteem and development)

Table 2. Potential Harms of Genetic Testing of Children

Medical (e.g. false-positive test results require further more invasive procedures)
Psychological (anxiety; diminished self-esteem)
Social (discrimination: loss of insurance and/or educational or employment options; stigmatization: knowledge of carrier status might distort the perception of the child by family members which might cause psychological maladjustment or stigmatization)
Autonomy-related harms (confidentiality is violated because parents know the results; autonomy to make the choice oneself is lost; in the case of mature adolescents, the decision to test might not represent the definite preferences of the future adult because stability of choice during adolescence as compared to adults is not clear)

complex because, in general, medical benefits are distinguished from other benefits and weighed differently (see Tables 1 and 2). Especially if psychological and social consequences are uncertain, there is a tendency to put the principle of "do not harm" first and to abstain from testing for which benefit has not been clearly proven while some risk of harm cannot be excluded. This attitude reflects what has been called the "principle of caution". It draws on the ethical imperative that children need to be protected since they are not in a position to decide for themselves. From this attitude follows that genetic testing is permitted only "a. when it is in the best interest of the child or b. when the legitimate interests of the parents or family can be promoted without anticipated harm to the child" (Committee on Bioethics et al., 2001). Although a protective and therefore cautious attitude seems justified, it is important to keep in mind that it has its limits. Overprotection, i.e. denying children potential benefits to avoid even the slightest risk of harm, is ethically problematic.

Since children depend on the protective decisions others take on their behalf, it is important to examine closely how these decisions are made. When deciding in favour or against testing of children, one will need to take into account potential pressures that might influence not only parents and professionals but also guideline makers themselves in a given context. It is well known that progress in medicine and biotechnology can create pressures to overuse new devices because these are seen as advanced and modern, although evidence on consequences is still scarce. Withholding these new technologies is often perceived as depriving individuals of available new options and this perception is nourished by biotechnology companies who will make benefit from the use of new testing and who might influence children advocacy groups (Paul, 2008). When balancing benefits and harms, it could be a sound reflex to be aware

of these mechanisms that might lead to an overestimation of potential benefits. On the other hand, in certain – often religious – communities, the opposite tendency is present, with a risk to be overly critical towards new technologies. Potential harms resulting from these technologies can be systematically overestimated on the grounds that they are seen in conflict with "natural" human functioning and destiny.

Special Standards for Adolescents?

Many jurisdictions allow competent adolescents to make their own health-care decisions (Sigman & O'Connor, 1991). From the ethical point of view, caution is urged if adolescents' decisions are judged harmful to themselves. Those who limit genetic testing for adolescents (Ross, 2000; Ross & Moon, 2000) would limit their choices also concerning other possibly harmful decisions such as the refusal of treatment at the end of life (Koogler, Wilfond, & Ross, 2003; Ross, 1997).

A number of ethical arguments exist to distinguish between genetic testing of children and genetic testing of adolescents. Competency as such is of major importance not only in legal frameworks but also in ethical approaches. Incompetent adults are denied the right to provide informed consent. According to research on children's decision-making abilities, sufficient evidence exists to come to the conclusion that 14-year-old adolescents reason as maturely as adults in medical decisions (Melton, 1983a). If adolescents are allowed to marry and to take other important health-care decisions, it is ethically incoherent to deny them the possibility to request genetic testing, unless it can be proven that the gene tests are disproportionately harmful compared to the risks related to other types of permitted decisions.

Even if one maintains that a difference exists between the maturity of adolescents and adults, based on the ethical approach of a "sliding scale" of competency, it is appropriate not to confound children with competent adolescents and to permit the latter to request at least certain types of genetic tests (Elger & Harding, 2000). The concept of a "sliding scale" of competency has been proposed by Drane (1985). The general aspects of this concept are widely agreed to in paediatrics (Committee on Bioethics, 1995): in the case of a very risky or harmful decision, the threshold for competency should be high. In decisions involving a lesser risk, we can admit a lower threshold for competency. Drane claims the highest standard of competence for decisions about very dangerous treatments and for decisions considered "irrational" by professionals and the public. Only for these types of decisions does he consider the legal age of maturity as being one of the prerequisites for competency. It seems exaggerated to classify carrier testing (Clarke, 1994) or certain types of predictive testing for adult-onset diseases as "irrational" (Elger & Harding, 2000).

This does not automatically mean that testing of adolescents is recommended but only that refusing such tests, for example of carrier testing, can be ethically unacceptable if the request is made by a an adolescent who meets conditions of competence, voluntariness and adequate understanding of information (ASHG/ACMG, 1995), who is "able to participate in the decision as an autonomous individual" (Clarke, 1994) or who has

"decision-making capacity" (American Medical Association [AMA], 1995). It might, however, be advisable that the adolescent has his parents' support (Borry, Fryns, Schotsmans, & Dierickx, 2006).

Balancing of Ethical Principles

It is important to notice that the balancing of benefits and harms takes place on several different levels. Guidelines, similar to definitions of a "medical indication", use a model of balancing that looks at average cases. Benefits and harms for genetic tests need to be generalized for typical or "normal" children and their families. This generalization is important and helpful. However, it has to be complemented by an evaluation of the benefit–harm ratio in each individual case, as far as this is possible. Indeed, when predicting consequences for individual cases, one will again have to refer to average results from studies on similar populations, while taking into account any factors that are known or suspected to influence outcome. The individual benefit–harm evaluation should consider not only individual factors but also variations within different social communities (Port, Arnold, Kerr, Gravish, & Winship, 2008). As the experience with screening for sickle cell disease among African-Americans has shown, the risks of genetic stigmatization and discrimination are significantly influenced by already existing discrimination and stigmatization of members of a given ethnic, racial or socioeconomic group. While in the case of sickle cell disease these risks might point towards abstention from testing, in communities with high socioeconomic status and low prior risk of discrimination, genetic testing might not cause significant additional social risks. Absence of adverse social consequences has been claimed to have resulted for example from the screening for Tay-Sachs disease in Ashkenazi communities (Boddington & Hogben, 2006; Broide, Zeigler, Eckstein, & Bach, 1993).

As psychosocial risks related to the same genetic test might vary according to the community in which it is carried out, they also depend largely on the potential of misunderstandings. Parents and communities who have not understood completely the meaning of "carrier status" or "false-positive results" might never lose the fear that tested children are affected by genetic disease. Therefore, even if in the best case scenario, risks of a genetic test are minimal, in a given community, misunderstandings may create significant risks. On the other hand, it is not justified to withhold testing in general only because in some circumstances misunderstandings created additional risks. Indeed it might not even be justified to withhold testing because of a risk of misunderstandings because these false perceptions can be changed through education and counselling.

The Entanglement of Family and Child Benefits

In the present ethical framework of "principlism" which has traditionally guided genetic counselling and the recommendations for the testing of minors, respect for autonomy, beneficence, non-maleficence and justice

are the prevailing criteria on which decisions are based. This principle-based approach emphasizes the rights of the individual child whose future autonomy and best interests need to be protected. The strong focus on individual autonomy implicit in contemporary bioethics leads to an approach-based relative blindness for the interactions between children's good and family's beliefs and values, as well as the parents' concern for their children (McConkie-Rosell & Spiridigliozzi, 2004). Indeed, in the ethical discussion about the benefits and risks of testing children, the benefit of children is most often evaluated separately from the benefit of other family members. However, it is well known that the physical and psychological well-being of parents and other family members has a significant influence on the well-being of children. It is therefore important to consider whether the refusal to test a child at the request of parents will cause anxiety or other adverse consequences in one or both parents that might affect the well-being of the child. In some situations the child could be better off being tested and living with a parent whose "nagging anxiety" (Duncan & Delatycki, 2006) has been relieved than not being tested and having future autonomy preserved, but suffering from psychological consequences induced by the parent's persisting anxiety. Indeed, empirical evidence exists indicating that the relief of anxiety in those who want to know for themselves and/or their children is mostly related to the relief of uncertainty and does not depend on whether the test result is positive or negative (Duncan et al., 2008; Wiggins et al., 1992).

Last but not least, thinking about families in terms of conflicting interests and opposing the benefit of children to the benefit of other family members could be misguided as it uses a too narrow notion of informed consent to medical procedures concerning children (Kuczewski, 1996). It could be more appropriate to view informed consent as a process of shared decision making adapted to the communication styles of the family. Involving children in the decision aims at helping the child clarify his or her values and preferences (Geller, Tambor, Bernhardt, Fraser, & Wissow, 2003).

Justice

The principle of justice, i.e. fairness and equity, is often much less cited in discussions about genetic testing. The reason seems to be that geneticists and physicians are influenced primarily by the principle "*first* do not harm". Hence, concerns of the medical profession are directed towards limiting harmful tests rather than towards facilitating fair access. Whereas the medical profession has some control over medical indications of tests, physicians perceive themselves as relatively powerless as regards questions about access to health care which is seen as a politically difficult issue, especially in the United States. However, individual practitioners should keep in mind that decisions about genetic testing of children should not be based solely on considerations about benefits and harms to individual children and their families but that they take place in a greater framework where the principle of justice matters.

Informing About Genetic Risks

Interestingly, while the question of genetic testing of children is addressed frequently, the issue of informing them about genetic risks running in the family receives much less attention in guidelines and ethical and legal publications. If testing is postponed until children reach the age of maturity, it seems to be taken for granted that parents will inform their children timely about genetic risks. The French National Consultative Ethics Committee for Health and Life Sciences (NCEC) stipulated that parents have the duty to tell their children about known and suspected genetic risks (National Consultative Ethics Committee for Health and Life Sciences, 1995). According to the NCEC, this information should be transmitted not when children reach the age of majority but rather when they reach the age to make reproductive decisions. Although most adolescents are not planning to have children, a sizable number of them will become pregnant voluntarily or accidentally. It could be argued that parents who did not inform their adolescent child about genetic risks due to diseases running in the family are infringing autonomous choices of at least some children. On the other hand, if adolescents are denied the possibility to request genetic testing after having been informed about genetic risks, one could argue that any information given before the age of 18 would only cause anxiety and worry to the child without offering a possibility to relieve uncertainty by undergoing testing (Malpas, 2006).

It is difficult to make recommendations about the age of informing children about genetic risks because the benefits and harms of telling them the truth depend on the individual family and the child. If many family members are ill, intelligent children are likely to have learnt in school about genetic diseases and will be able to come to adequate conclusions in light of the hereditary pattern of the disease. In addition, adults often underestimate the ability of children to feel that important information is hidden from them. As L. Tolstoi has depicted in a haunting novel, a patient or a child might suffer more from being excluded from information shared by all others than from knowing the bad news (Tolstoi, 1961).

Since the balancing of ethical principles, and especially of benefits and harms, depends on many factors such as the genetic disease, the available evidence, the cultural context and the individual family situation of each child, it is important to examine how the general principles discussed above apply to particular types of testing and to individual cases.

NEWBORN SCREENING

The ethical justification of newborn screening should take place at two different levels: first, from a public health perspective, it needs to be decided whether a particular gene test should be offered as part of a generalized screening program and how the participation in these programs can be ensured. Second, although generally indicated, at the level of individual cases, newborn testing might still cause ethical problems, as well as practical problems. To provide an example for practical problems,

testing for PKU is efficacious only if the state follows up with medical care and makes sure that parents can afford the expensive diet.

Therefore, ethical standards should be used to decide in individual cases whether refusal of participation in a newborn screening program is appropriate or at least acceptable. On the other extreme, in some cases, widely offered newborn screening might not be sufficient and other genetic tests should be added.

A comparison between newborn screening in different countries and different States in the United States shows that a great variability exists with regard to how many and which tests are included. This reflects to what extent the judgement about whether and which tests are appropriate from a public health perspective and from an ethical point of view is controversial. At the public health level, the first ethical concern should be whether the identification of the genetic disease in the newborn is beneficial without adding disproportionate harm. Screening is beneficial if testing permits to detect newborns with serious, treatable disorders so as to initiate appropriate interventions to prevent or alleviate adverse outcomes (Ardaillou & Le Gall, 2007). This implies that "a test with appropriate sensitivity and specificity is available" which permits to identify the disease "at a period of time (24–48 h of birth) at which it would not ordinarily be clinically detected" (ACMG, 2004).

Extending newborn screening to untreatable conditions such as fragile X syndrome is ethically problematic (Bailey, Skinner, Davis, Whitmarsh, & Powell, 2008). Newborn screening (NBS) for fragile X syndrome (FXS) could imply some medical benefits for the baby. Studies have shown that although families often suspect developmental problems by 12 months of age, a diagnosis of developmental delay is often delayed until the child is almost 2 years old. The child is often nearly 3 years old when finally the diagnosis of FXS is made. This implies that children have not had the opportunity to benefit from early intervention as they could have if their condition had been identified through newborn screening (Bailey et al., 2008).

The example of FXS illustrates the ethical controversy about the weighing of different types of benefits. For FXS, newborn screening could be beneficial for reproductive decisions of the parents. When symptomatic children are diagnosed with FXS at the age of 3 years, during these 3 years their parents often have additional children with FXS since they are not aware of the reproductive risk. These "parents report frustration with professionals and the health-care system, strongly support voluntary NBS for FXS and consider advantages of screening more likely than disadvantages" (Bailey et al., 2008; Bailey, Skinner, & Sparkman, 2003; Skinner, Sparkman, & Bailey, 2003). The expert group commissioned by the American College of Medical Genetics distinguished between primary interests and secondary interests that justify newborn screening (ACMG, 2004): "Newborn screening policy development should be primarily driven by what is in the best interest of the affected newborn, with secondary consideration given to the interests of unaffected newborns, families, health professionals, and the public" (p. 27). However, the place given to secondary considerations is difficult to determine. The controversial

balancing of the conflicting interests explains the variability in conditions included in state newborn screening panels (Koopmans, Hiraki, & Ross, 2006). More generally, ethical issues of testing for untreatable diseases that manifest themselves in childhood as well as predictive testing for different types of diseases (diseases where treatment or prevention is available in childhood versus untreatable adult-onset diseases or those where treatment of prevention is indicated after the age of 18) will be discussed below in separate sections.

In the case of conditions for which treatment or prevention is available, the balance between benefits and harms varies not only for different diseases but also for different tests for the same disease if they imply different percentages of false-positive and false-negative results. Testing for cystic fibrosis (CF) illustrates the ethical standards that have guided public policy making. Medical benefit of newborn testing, for example better prognosis of the disease if it is diagnosed early, has been controversial in the beginning but seems to have been at least partly confirmed recently through randomized trials (Balfour-Lynn, 2008). Benefits need to outweigh clearly possible harms of the screening. In CF, missed cases, the so-called false-negative results are found in 2–4% in the United States (Balfour-Lynn, 2008). This means that in 2–4% of cases, harm might result from the fact that diagnosis is unduly delayed. False-positive results are found in a certain percentage of carriers of a CF mutation, i.e. children who will not develop the disease. These results have caused harm because even 1 year after the test and in spite of repeated counselling, a significant number of parents continued to believe that their child is ill or will become ill. Interestingly, some evidence exists that carriers are at increased risk of some types of pulmonary disease (Balfour-Lynn, 2008). In addition, stigmatization is not excluded since a carrier status matters for reproductive decisions and could be considered as a handicap for marriage or, more generally, as a handicap for finding a partner and/or having children.

Ethical considerations related to benefit go further than the simple test result. Testing will be beneficial only if newborns and their parents have access to appropriate health-care services that permit providers to confirm the diagnosis and to identify false-positive results. Hence, treatment and follow-up services must be available in order to justify newborn screening (Lloyd-Puryear et al., 2006).

In addition to the benefit for the child, newborn screening programs need to fulfil criteria that can be described as public health benefits. Cost effectiveness for society is a complex issue (Clayton, 1999) and this criterion should be complemented by public participation through democratic political institutions (President's Commission, 1983). Overall, the balancing of benefits and harms in newborn screening for CF does not yield indisputable results. It is therefore not surprising that 22 out of 52 States in the United States as well as a number of European countries (e.g. Germany, Holland and Switzerland) have not implemented this type of screening (Balfour-Lynn, 2008).

An important feature of ethical standards that are largely influenced by benefit–harm evaluations is the fact that evaluations might change according to advances in medical knowledge and results from empirical

studies. As a consequence, regular evaluation of the benefit–harm ratio of established screening programs is ethically warranted (Newborn Screening Task Force, 2000).

At the individual level, ethical reasons might exist not to proceed with newborn screening if harms are perceived to be disproportionately high as compared to the expected benefits. The most frequent example where comprehensive ethical standards should be used to complement public health decisions is parents' refusal of newborn screening. Ethical analysis extends in this context to the balancing of benefits and harms concerning not only newborns but also more global societal benefits and harms. Screening programs such as newborn and carrier testing have stirred ethical controversy as to whether they should be mandatory or voluntary. It could be argued that if tests are beneficial, they should be mandatory in order to protect children against forgoing this benefit because of parents' refusal. However, mandatory programs by itself have high ethical costs in terms of the human rights issues raised by coercion (Wilfond & Nolan, 1993). Using force has adverse consequences on the functioning of a society and on trust in authorities. In paediatrics, coercion of parents is justified only in exceptional cases if parents' decisions imply significant, life-threatening consequences for children (Committee on Bioethics et al., 2001). Mandatory testing would also threaten the overall benefits of newborn screening which rely on follow-up and treatment of the identified conditions and parental education. This will be effective only if parents trust health-care providers and collaborate willingly in a voluntary setting using informed consent or informed dissent. In the latter, parents are permitted to refuse testing of their newborns after having received detailed information (Fant, Clark, & Kemper, 2005). In summary, voluntary programs based on thorough information and education are ethically preferable because they are globally more beneficial.

CARRIER TESTING AND CARRIER SCREENING

In the case of autosomal recessive (e.g. sickle cell anaemia, CF, thalassemia major, Tay-Sachs disease) and X-linked disorders (e.g. muscular dystrophy) and in certain balanced chromosomal rearrangements, carrier tests permit to identify individuals who carry a mutated gene or a balanced chromosomal rearrangement. In these diseases, heterozygous carriers are in general healthy. Hence, carrier testing does not imply a direct medical benefit for the screened individual. However, together with appropriate counselling, it permits informed reproductive choices. The range of choices is larger if testing is done before any sexual activity takes place as compared to testing during pregnancy.

Carrier testing in minors is one of the issues in which geneticists, physicians and parents disagreed most in the past. While both the UK working group (Clarke, 1994) and the Genetic Interest Group favoured postponing presymptomatic testing of children for adult-onset diseases, the Genetic Interest Group opposed the recommendation of the working group to defer carrier testing until the age of majority (Dalby, 1995).

Parents of a child that has just been diagnosed with a particular condition claim the right to know whether any of their other children is affected or is a carrier. They think that responsible parents might want to make sure that their children are not treated differently because some know their genetic diagnosis and some do not. Parents also would like to ensure that their children have sufficient time to integrate genetic information into their personal identity. Others in favour of carrier testing during childhood believe in family cohesion and think that all members of a core family affected by genetic disease benefit from sharing the knowledge and the burden of the disease.

Potential benefits and harms of carrier testing in children are summarized in Table 3. There might be a risk to underestimate psychological harms for a child resulting from learning to be a carrier on the grounds that carriers are healthy and therefore the consequences of testing are limited to the positive effect of increasing reproductive choices. At least in community screening programs for carrier status, however, it has been discovered that receipt of the information to be a heterozygous carrier has been associated with more distress and anxiety than previously assumed

Table 3. Benefits and Harms of Carrier Testing of Children (If Test Done in Childhood as Compared to After the Age of 18)

Benefits from testing
Public health benefits (increases the likelihood that the entire family is tested; greater probability to avoid future homozygote children; implementation of programs in school makes it easier to reach all children born in the same year; it is, however, not well defined whether and if yes to what extent testing in children or adolescents will influence future reproductive behaviour)
Social and autonomy-related benefits: increase in reproductive choices (if the testing is done before sexual activity starts: having healthy children, increased autonomy in decision making)
Psychological benefits for the child (possible, but not proven, better adaptation to carrier status enabling children to adjust to the information before they need to make choices about marriage and reproduction)
Psychological benefits for the child and the family (improvement in communication within the family, decrease in parental uncertainty and concerns about carrier status)
Harms from Testing
Psychological harms (possible, but not proven, greater psychological vulnerability to the stigma of being a carrier: decreased self-esteem, etc.)
Social harms (possible, but not proven, decreased choice of future partners because of stigmatization; the perception of the child by family members could be distorted by the knowledge of the carrier status and this could cause psychological and social maladjustment)
Financial harms (in principle, these harms should not result, unless misunderstandings exist about the meaning of the carrier status)
Autonomy-related harms (confidentiality is violated since parents will know about the test results, unless confidentiality is preserved in the case of competent adolescents; the children's autonomy to make the choice themselves as an adult is lost; if decisions are made by competent adolescents, it is not clear to what extent these choices are stable and representative of the choices of the future adults; if test results are obtained in earlier childhood, there is no guaranty that parents will make sure that children will receive this information when they reach the age of majority)

(Marteau, 1995; Senior, Marteau, & Peters, 1999). What distinguishes psychological and social harms in carrier testing from such harms in presymptomatic testing is the fact that carriers might not only be discriminated and stigmatized concerning reproductive questions but also be erroneously considered ill (as observed in the past) although heterozygote carriers' health is not affected by the carrier status.

In the following we will discuss separately the ethical, legal and social issues of carrier testing in individual children and of carrier screening programs.

Carrier Testing of Individual Children

Compared with predictive testing of children for adult-onset diseases, and to a lesser extent with carrier screening, the issue of carrier testing of individual children has been the focus of much less publications discussing the ethics and regulation of such tests (Borry et al., 2006; Davis, 1998).

Consensus exists that no reasons exist to test newborns for carrier status (Institute of Medicine, 1994; Nelson et al., 2001). According to recent guidelines (Institute of Medicine, 1994; Nelson et al., 2001), parents should be informed about the carrier status of a newborn child only if the result is obtained incidentally and if patients have been informed previously about this possibility and have received adequate education. In this respect, some softening of earlier guidelines took place following the implementation of newborn screening programs. In 1996, the American Medical Association advised that parents should not be informed about carrier status of their children that was found incidentally (AMA, 1996). Similar recommendations were issued by the German Society of Human Genetics in 1995 (German Society of Human Genetics, 1995a). Both professional guidelines proposed that discussion about the carrier status should take place with the child when he or she reaches the age to make reproductive decisions. Nowadays such practice finds probably less support because it implies a number of practical problems and an increased risk that this information is lost or that it cannot be kept confidential. Indeed, the guidelines from the American Medical Association suggested that the information about the carrier status of the child should be stored in a separate section of the medical record. It was hoped that this would help to prevent accidental disclosure. However, the mobility of US citizens could easily mean that a medical record from one place does not follow the patient to future addresses. In addition, patients have the right to see the content of their own medical record and parents have the right to consult the records of their children. It is therefore unclear how part of the medical record could be concealed. Finally, no control mechanism exists to implement the ultimate time of disclosure of this information and to define who should be in charge of this task.

Carrier testing, as compared to carrier screening of entire populations, means that the tests are offered to children with a family history of a disorder where carrier testing is an option. As compared to testing of newborns and young children for carrier status, carrier testing in older children and

adolescents cannot be ethically rejected in the same outright way and needs a more differentiated approach. Among authors of guidelines, in line with the cautious approach adopted for all gene tests in childhood, consensus exists that the general rule should be not to test minors for carrier status (Borry et al., 2006).

The general attitude to be taken with parents and children in carrier testing is to discuss openly the alternatives and the ethical arguments because the best guarantee to avoid negative psychosocial consequences is adequate education and consensus between physicians, parents and the child about the approach, be it the testing or the deferring of the test until the age of majority. Testing might be justified on the grounds that the results of a carrier test performed during childhood will affect not only the future of the tested child but also that of his parents or other siblings. If consequences affect solely the child, his or her personal choice and consent should take precedence over the wishes of third parties (Borry et al., 2006).

Although since 1994 those having to issue recommendations have complained about the dearth of evidence concerning negative and positive consequences of testing in childhood (Clarke, 1994), there have been very few studies during the past 15 years that added data helpful to guide decisions (Jarvinen et al., 1999, 2000; Jarvinen, Lehesjoki, Lindlof, Uutela, & Kaariainen, 2000). The lack of data might not be surprising if one takes into account that with respect to carrier testing many would not give precedence to psychosocial consequences as such but to the preservation of a child's autonomy. According to this view, the evidence-based proof that carrier testing in childhood is not harmful would still not be considered a sufficient ethical reason to allow for testing (Borry et al., 2006). Neither would proven absence of harm give parents a legal right to request testing during childhood (Clayton, 1995). Indeed, the absence of harm caused by the testing does not matter for those who believe that the overriding reason for not testing children is to preserve their autonomy and confidentiality. Reproductive decisions are among the most personal and private choices to be made in life. If carrier testing has an impact only on reproductive decisions of the child, he or she should be able to take these very personal decisions alone. Children should be allowed the choice as to whether they would like to be tested and as to whether they want their parents to know about their test results. It could be argued that this view is typical for a society that gives priority to individual rights and that does not consider families as entities in which the general presumption is that happiness and burdens are shared. Unfortunately, we did not find any data that indicate whether families prefer sharing of knowledge about genetic disease or not. However, existing studies let us presume that at least in a core family, sharing of knowledge by children with their parents is more widely found than the concealing of information, especially if children know that their parents who are themselves carriers would like to know.

Which are the exceptions where carrier testing during childhood may not only be ethically defended but where withholding the tests could even be considered ethically wrong?

First of all, there are good reasons to allow carrier testing of a child when a newborn sibling of this child is identified as being a carrier. How should it be explained to the parents that it is justified to inform about the carrier status of the newborn, whereas a similar test in the older child is not allowed until this second child reaches the age of maturity (Borry, Nys, & Dierickx, 2007)? Not only might the differential treatment of two children in the same family be condemned as inequality, but also the inconsistency could lead to a distorted perception of one or both of the children by family members and imply the risk of psychological maladjustment or lead to privileged treatment of one child and discrimination of the other. Of course, if the older child happens not to be a carrier, the newborn might be treated differently, but this is not fundamentally different from the inequality in risk before the test.

Another exception in which testing of minors for carrier status can be justified is when the test is requested by minors themselves who are judged to be capable of taking their own decisions. The criterion used to define the appropriate age in this respect varies. As the main reason for testing is to influence reproductive decisions, it might seem logical to propose as threshold the fact that minors need to be of reproductive age (AMA, 1995; German Society of Human Genetics, 1995a), where the test result could therefore influence their own behaviour. The American Academy of Pediatrics (AAP) is even more restrictive and considers carrier testing appropriate only if an adolescent is pregnant or is planning a pregnancy. The underlying assumption is that most adolescents who are of reproductive age are not concerned about reproductive decisions and if they become pregnant, it is accidental. Hence, knowledge about carrier status would not have influenced their decisions.

However, even if it can be shown that the majority of adolescents' reproductive decisions will not be affected by the knowledge about being a carrier, this does not provide an ethical reason for not taking into account the wishes of the minority of adolescents who want to know. In line with ethical and legal standards, it is more straightforward not to use reproductive age or reproductive plans as the major criterion, but to refer, as most guidelines do, to the child's competence, i.e. the ability of the child "to understand and decide for himself" (National Consultative Ethics Committee for Health and Life Sciences, 1995), to "participate fully in the decision" (Bioethics Committee Canadian Paediatric Society, 2003) or "to make an informed decision" (European Society of Human Genetics [ESHG], 2001). Any adolescent must be informed about the risks and benefits of testing before taking his or her decision. It does not seem ethically justified to prohibit testing, although it is possible and according to the situation advisable to depart from the idea of non-directive genetic counselling and to try to persuade the adolescent to defer the test until he or she reaches majority. Although there is no obligation for physicians to provide diagnostic procedures or treatment to patients without medical indication (Brett & McCullough, 1986; Youngner, 1988), ethical reasons could mandate not to refuse testing. The principles that would allow for testing in these cases are the respect for autonomy, i.e. the respect of the right to make reproductive decisions, and non-maleficence if testing can prevent the minor from having affected children which could cause

suffering for him/her and his/her offspring. Affected communities have themselves judged carrier testing of adolescents as overall beneficial or at least as not harmful enough to warrant prohibition. This is best shown by the fact that carrier testing for recessive diseases has been part of high school testing at the request of communities in the past (Gason, Aitken, Delatycki, Sheffield, & Metcalfe, 2004; Gason, Aitken, Metcalfe, Allen, & Delatycki, 2005; Gason, Delatycki, Metcalfe, & Aitken, 2006; Gason et al., 2005, 2003).

A few guidelines admit exceptions for testing in cases where the result has implications for family members. The more restrictive view is that testing is allowed if it implies significant medical benefit to a relative, for example if it provides haplotype information (AMA, 1995; ESHG, 2001). Others define benefit to a relative more widely. They give more weight to psychosocial benefits for parents on the grounds that family dynamics does not permit to separate the benefit of children from that of their parents and siblings (British Medical Association, 1998; Dalby, 1995). According to this view, refusing carrier testing after persistent request to a parent when uncertainty about the carrier status is harming the entire family is not ethically justified. Indeed, empirical evidence exists that uncertainty can be psychologically more harmful than certainty even if the news is worse than confirmation to be a healthy carrier of a recessive mutation, e.g. if the testing confirms the genetic predisposition to Huntington's disease (Wiggins, Green, Adam, & Hayden, 1996; Wiggins et al., 1992).

Concerning testing of children, it should be noted that the law had so far "little to say" about how these dilemmas should be resolved by physicians, parents and children concerned. It does not give a constitutionally protected right to parents to request testing. In general, physicians do not have to fear liability for damages if they accept or refuse testing of children for carrier status unless a child suffers from physical harm that has been caused by the physician's decision not to test or that has not been disclosed as possible risk before the test was ordered at the request of parents (Clayton, 1995). A recent court case, Molloy versus Meier (Burke & Rosenbaum, 2005), found a physician liable for not having reported the results of a test for fragile X syndrome in a 3-year-old child with developmental delay. The parents had suspected genetic disease and asked for genetic testing of their first child in order to guide planning of further pregnancies. Mrs. Molloy gave birth to another affected child and claimed that the negligence of the physician had caused damage to her and to the second affected child ("wrongful birth"). It is not clear how this case would apply to carrier testing for diseases that do not manifest in childhood. If the hereditary disease running in the family is known or suspected, reproductive decisions of couples could be made by testing the parents without the need for testing an unaffected child.

Carrier Screening Programs for Minors

Carrier screening programs have so far been proposed for older minors during high school. They were restricted to few diseases and distinct populations, mostly sickle cell anaemia in African-Americans and Tay-Sachs

disease in Ashkenazi Jews (Kenen & Schmidt, 1978; Ross, 2006). Such programs add ethical, legal and social issues different from carrier testing in affected families, in particular because public health considerations are involved.

The intention of carrier screening programs is to increase benefit for individuals and for society. The challenge is to offer cost-effective programs, including expert counselling and follow-up to all members of a society who may benefit. In order to do so, confidentiality and freedom of choice need to be ensured, while misunderstanding and stigmatization must be avoided (Rowley, 1984). Although reducing the incidence of genetic diseases is a legitimate public health goal, programs are not justified if this is their sole aim. Such practice is judged too close to eugenics because possible harm can result from testing and autonomous choice is threatened. The principal objective of screening programs should be to "maximize the options available" to individuals at risk (Rowley, 1984). In line with this objective, it is justified to try to reach the largest uptake of a screening test if knowledge is judged to be beneficial for a population. High school testing was preferred because it yielded an uptake of 27.6%, compared to 20.1% among college students and 10.8% among recently married couples (Beck, Blaichman, Scriver, & Clow, 1974; Clow & Scriver, 1977; Scriver & Clow, 1990; Zeesman, Clow, Cartier, & Scriver, 1984). Moreover, the programs in high schools had the advantage of being able to inform entire birth cohorts about genetic diseases. Offering information is important since "[n]ot being tested because one is unaware that carrier testing is available, or because one is unaware that one is at risk [. . .] is ethically problematic" (Ross, 2006). However, testing in high school poses a number of ethical problems that have influenced decision makers to abandon such programs in a number of cases. The examples of existing programs show that the balance of positive and negative consequences of high school and other population-wide carrier screening varies widely and depends to a large extent on pre-existing vulnerabilities of certain populations such as racial discrimination against African-Americans, or poor education and rigid marriage rules in certain rural populations in Greece (Kenen & Schmidt, 1978). If screening targets populations based on race, ethnicity or religion, individuals should have the option to participate voluntarily. Confidentiality must be strictly ensured in order to minimize stigma. Some authors argue that neither in multi-ethnic schools nor in parochial schools can both conditions be achieved. In addition, although carrier testing can be justified in individual cases (see above), it has not been recommended on a large scale due to the risk that learning about one's carrier status in adolescence when sexual identity is formed can have an adverse impact on self-identity (De Braekeleer & Melancon, 1990; Denayer, Welkenhuysen, Evers-Kiebooms, Cassiman, & Van den Berghe, 1996, 1997; Evers-Kiebooms, Denayer, Welkenhuysen, Cassiman, & Van den Berghe, 1994; Evers-Kiebooms, Welkenhuysen, Claes, Decruyenaere, & Denayer, 2000; Melancon & De Braekeleer, 1996; Welkenhuysen et al., 1996). Hence, for ethical reasons, it has been advised that carrier screening programs should target young adults rather than high school students even if this means that uptake is lower.

The most important lesson to be learnt from past carrier screening programs for minors is that one should not generalize. Distinct diseases, distinct populations and distinct settings (rural versus urban, etc.) can have completely different implications for the programs and result in a different balance of benefits and harms. Social issues matter insofar as the imposition of screening from without a community is ethically more problematic than instigation from within (Boddington & Hogben, 2006; Hogben & Boddington, 2006). Recommendations that are made on the grounds of examples of diseases without mentioning these relevant social and political differences are themselves ethically problematic. Communities themselves have developed interesting strategies to avoid stigmatization and discrimination. In some Jewish communities, carrier status has not been disclosed directly; rather, pin numbers have been created that permit to identify cases where two potential marriage partners are both carriers.

It can therefore be concluded that although arguments speak in favour of using alternatives to screening minors, some diseases and support from affected populations can justify programs that involve participation of competent minors.

ETHICAL PROBLEMS IN PREDICTIVE GENETIC TESTING FOR DISEASES WITH CHILDHOOD ONSET WHERE NO TREATMENT OR PREVENTION EXISTS

Symptomatic diagnostic genetic testing in minors is a widely accepted part of routine medical care. For example, a standard medical work-up for a child with developmental retardation includes testing for fragile X syndrome (Park, Howard-Peebles, Sherman, Taylor, & Wulfsberg, 1994). Incomplete genetic testing of symptomatic children can even lead to law suits if parents claim that the missed genetic diagnosis has led to the birth of another affected child (Burke & Rosenbaum, 2005).

However, once in a family one child is diagnosed with a genetic disease, new ethical issues are raised. Parents and medical professionals have to deal with the fact that other family members could be affected, although still without symptoms, or carriers. It is at present controversial whether and when testing of asymptomatic children is indicated who are at risk for developing a disease in childhood for which no treatment or prevention exists. Testing could be indicated in order to avoid future delay in diagnosis and multiple unnecessary tests (Bailey et al., 2008).

The following example illustrates the ongoing ethical debate in cases where medical benefit of testing has not been proven and psychological benefits and harms are largely unknown. The Li–Fraumeni syndrome (LFS) is a rare familial cancer syndrome. It is caused by germline TP53 mutations which predispose to the early onset of multiple cancers including childhood adrenocortical carcinomas, sarcomas and brain tumors, and breast and colon cancers in young adults. Genetic testing of unaffected children for TP53 mutations in families affected by LFS has been so

far rare since the testing does not imply direct medical benefit (American Society of Clinical Oncology [ASCO], 1996; Patenaude, 1996). Testing takes place mostly after children have been diagnosed with target cancers and the family history suggests the presence of LFS. Because of the absence of validated risk reduction strategies in this disease, geneticists and oncologists disagree on how requests of parents for the testing of children should be handled (Prochazkova, Foretova, & Sedlacek, 2008). The American Society of Oncology (ASCO, 1996) and the British Society for Human Genetics (Clarke, 1994) argue against the right of medical professionals to refuse testing because parental authority to decide for or against testing this group of children should be respected if the medical community holds controversial views about the indication of testing (Borry et al., 2006). However, the role of cancer genetics professionals as advocates for the best interests of the child should imply that parents are informed about the existing arguments against testing before making their decisions.

ETHICAL PROBLEMS IN PREDICTIVE TESTING OF CHILDREN FOR DISEASES WITH CHILDHOOD ONSET FOR WHICH MEDICAL INTERVENTIONS ARE AVAILABLE

Guidelines and position papers published between 1991 and 2005, penned by 31 different professional organizations, agree that presymptomatic and predictive genetic testing in children is justified if medical interventions or preventive measures are beneficial during childhood. All guidelines recommend that testing should be postponed when medical intervention or prevention is not urgent in order to permit the competent adolescent or adult to take his or her own decision. Examples for diseases where childhood testing is judged acceptable are familial adenomatous polyposis (ASCO, 1996; Codori et al., 2003), multiple endocrine neoplasia (MEN) such as MEN type 2 syndromes (ASCO, 1996) and inherited cardiovascular diseases such as hypertrophic cardiomyopathy or channelopathies (Charron et al., 2002; Smets et al., 2008).

In spite of the relative consensus among guidelines, a number of ethical problems persist. The place of psychological benefits as justification for presymptomatic testing in childhood remains largely undefined. Most guidelines refer to “medical benefits” leaving unclear whether favourable mental health outcomes could count as medical benefits. The ASHG/ACMG report about genetic testing in children and adolescents (ASHG/ACMG, 1995) mentions both medical and psychological benefits (“if medical or psychological benefits of a genetic test will not accrue until adulthood, as in the case of...adult-onset diseases, genetic testing generally should be deferred”). Even if the criterion of psychological benefits is taken seriously, the problem persists that presently there is not enough evidence to define the psychological consequences of presymptomatic testing in children. In line with a cautious approach, the absence of proof for adverse psychological consequences is insufficient. Instead strong

evidence for positive psychological consequences would be needed to provide an argument for testing.

Another ethical and social problem of testing children for diseases with childhood onset for which medical interventions are available is that the meaning of a positive test is not always clear to parents and their children. Studies showed that when children were tested for the *RET* gene for MEN2, almost one-third of their parents believed that the test would indicate if their child had the disease rather than assessing genetic predisposition (Grosfeld et al., 2000; Patenaude, 1996). This problem underscores to what extent the ethical justification of testing will depend on the context including not only adequate counselling of parents but also the thorough verification of how much of the information has been understood correctly.

Which is the best timing for the tests? Guidelines recommend testing if the results are of "immediate" relevance (Human Genetics Society of Australasia, 2005; Swiss Academy of Medical Sciences, 1993) for the health of a child or may offer "timely" medical benefit (ASHG/ACMG, 1995). This refers in general to the moment where preventive or therapeutic measures need to be started and where testing is beneficial because unnecessary screening can be avoided in children who do not carry the mutation. The "rule of earliest onset" (Kodish, 1999) has been advocated on the grounds that a long period of time between the request for testing and the estimated onset of symptoms could imply adverse consequences for the children and would therefore not be in their best interest. However, the Genetic Interest Group, a UK alliance of patient organizations (Dalby, 1995), claimed that parents should be given the possibility to decide about the best moment of such testing. This group defended the idea that the ultimate responsibility for the welfare of children should be attributed to their parents. The Genetic Interest Group claimed that compared to those outside the family such as health professionals, parents are in a better position to decide on how to serve adequately the best interest of a particular child and of the family as a whole. Indeed, if the onset of the disease is before the time children reach competency, the argument to preserve their autonomy until they can decide for themselves loses its relevance. If parents have informed younger children about their risk to be a mutation carrier, it could be justified to let younger children participate in the decision on when to test because the knowledge to be at risk is itself a cause of anxiety and these worries could be relieved, at least in those children who will test negative for the disease-causing mutation. Since the consequences for testing earlier and for testing later will depend on the situation, dynamics and communication styles of each family, it is ethically sound to take parents' wishes and arguments seriously and refuse testing only if strong indication exists that children will be harmed by the premature testing.

In some diseases, screening can provide some medical benefits while at the same time being ethically contentious because of adverse social consequences (Berg et al., 2007). In X-linked androgen insensitivity syndrome (AIS), 46,XY individuals are unresponsive to androgens due to mutations in the gene encoding the androgen receptor (AR). These genetically male individuals present with an undervirilized (partial AIS) or

completely female external phenotype (complete AIS). Testing is medically indicated because of the known health risks associated with AIS. These include an increased risk of testicular neoplasms. Prophylactic gonadectomy is in general part of the treatment of these patients. However, in the absence of consensus guidelines, the most appropriate time for performing this procedure is unclear (Berg et al., 2007). Since androgens are also implicated in the regulation of bone mineral density, individuals with complete AIS are at risk for osteopenia. Testing is done most of the time once symptoms are detected. This is the case in childhood when an inguinal hernia reveals testicular tissue, in adolescence when amenorrhea persists or later in adulthood when infertility is evaluated. If AIS is diagnosed in a family because of one affected individual, if and when other family members should be informed about the disease and tested is controversial (Conn, Gillam, & Conway, 2005). Testing might have implications for future reproductive options in affected individuals and for reproductive choices in carriers. At the same time, it is not clear whether asymptomatic children will psychologically and socially benefit from growing up with the knowledge of their genotype–phenotype gender difference. Geneticists were concerned about possible adverse social consequences of testing after having identified "a surprising precedent related to the legal definition of sex" (Berg et al., 2007). In Littleton versus Prange (1999), a Court of Appeals in Texas nullified a transsexual woman's marriage to her deceased husband on the grounds that she was born with a 46,XY chromosome complement. Although she had a female phenotype and had lived as a heterosexual female throughout her life, it was ruled out that her chromosomal sex is decisive and as a male person her marriage to a man was invalid. We will limit here the discussion of testing children for AIS to presymptomatic testing (see above for the ethical issues of carrier testing). For minor children, testing could be indicated in order to prevent distress and confusion and to ensure social support. Children need to know about their condition before they are confronted with discussions about menstruation and before they engage in sexual activity. According to their age, it is also in their best interest and in line with respect for their (growing) autonomy to participate in decisions about medical management that cannot be postponed until they reach the age of majority.

PREDICTIVE TESTING OF MINORS FOR ADULT-ONSET DISEASES

The Ethical Dilemma

Several studies have shown that a sizable percentage of geneticists and paediatricians test or would be willing to test children for adult-onset diseases at the request of parents (Clarke, 1994; Demmer et al., 2000; Duncan, Savulescu, Gillam, Williamson, & Delatycki, 2005; Wertz, 1998; Wertz & Reilly, 1997). If the request emanates from an adolescent who is legally in the position to ask for a predictive genetic test, clinical geneticists are significantly more willing to carry out the testing,

particularly if the minor's parents join the request of their child (Borry et al., 2008). Predictive testing of children for adult-onset diseases is ethically controversial if the child is asymptomatic and if testing does not provide any medical benefit concerning treatment or prevention. Typical examples are testing of children for Huntington's disease or hereditary breast and ovarian cancers. Guidelines published by several medical professional organizations as well as by patients' or parents' interest groups show consensus. They recommend that individuals who have not reached the age of majority should not be tested for hereditary late-onset diseases (Dalby, 1995; German Society of Human Genetics, 1995b; International Huntington Association, 1994).

Huntington's disease (HD) and hereditary cancer linked to *BRCA1* mutations are the classical and best studied examples of hereditary diseases that manifest themselves in adulthood. Hereditary breast cancer linked to the *BRCA1* gene is, like HD, an autosomal dominant disease with onset in adulthood. In some cases, early manifestation may occur in the twenties. In contrast to HD, hereditary breast, and to a less extent, ovarian cancer can be treated or prevented with variable success, but both treatment and prevention need to be started only during adulthood.

Significant efforts have been made to understand the consequences of predictive genetic testing in these diseases (Broadstock, Michie, Gray, Mackay, & Marteau, 2000; Broadstock, Michie, & Marteau, 2000; Marteau, 1995; Michie, Bobrow, & Marteau, 2001; Michie, French, & Marteau, 2002). A growing number of publications discuss the ethical problems related to genetic testing in childhood. While in the past, statements against predictive testing of minors predominated (Fryer, 1995, 2000; Ross, 2000, 2004; Wertz, Fanos, & Reilly, 1994a, b), recently a number of authors have defended testing under certain conditions (Pelias, 2006; Rhodes, 2006; Robertson & Savulescu, 2001) or for certain sub-groups of adolescents (Elger & Harding, 2000).

The argument most often used not to test before the age of 18 refers to the absence of benefit for medical interventions or prevention in childhood (ASHG/ACMG, 1995; Clarke, 1994; Collins, 1996). The authors of the ASHG/ACMG report (ASHG/ACMG, 1995) have admitted that tests could exceptionally be allowed for some adolescents that are found to be sufficiently competent. They seem to imply that there would be few exceptions. In order to resolve the ethical dilemma, the ASHG/ACMG board of directors proposed two ways to justify exceptions. The first relies on the evaluation of competence, voluntariness and adequate understanding of information by the adolescent. Since "these issues are not always straightforward", the authors of the guidelines defined a second mechanism which is procedural: benefits and harms, as well as decision-making capacity and voluntariness, should be evaluated not only by geneticists but also by several other professionals such as paediatricians, psychologists and/or an ethics committee. A similar case by case approach has been argued from a legal perspective (Hoffmann & Wulfsberg, 1995). From an ethical perspective, it is difficult to defend parents' or practitioners' "right to withhold information" if a competent adolescent asks for testing (Sharpe, 1993), unless it can be shown that testing is contrary to the autonomous

choices of the future adults, i.e. that most adolescents would change their mind later in life and regret having undergone the tests. Moreover, since testing can be useful for reproductive decisions and life planning, individuals could be harmed if they have to wait until the age of 18. The best interest argument used by guideline makers to recommend against testing of children for adult-onset diseases leaves room for different opinions. The dilemma among others is due to the fact that in the classical case of a pre-test risk of 50%, statistically half of the tested children and their parents can be relieved from their anxiety and any fears of stigmatization and discrimination, whereas the other half could be at increased risk for these adverse consequences after having tested positive for the mutation. Asking for testing if there is a 50% chance of being better off after the testing than before can be characterized as a reasonable attitude. In addition, best interest is difficult to determine because even in the case of a test result confirming the mutation, some or even many of the tested children might experience some relief or at least not be harmed. Those in favour of testing children have referred to the possible harm caused by uncertainty and withholding information (Cohen, 1998; Rhodes, 2006). In addition, in untested individuals, a possibility of later misdiagnosis exists (Bradbury et al., 2008). Potential negative consequences could be outweighed by the concomitant positive value of testing due to the fostering of autonomy and increased ability to make informed life plans (Elger & Harding, 2000). Indeed, the cautious approach to testing could reflect paternalistic attitudes of physicians that have in the past proven to be contrary to patients' wishes. The Hippocratic principle "primum non nocere – first do no harm" has been traditionally cited as reasons by physicians for not informing patients about the nature of their illness. It took many years for patients and their organizations in North America and West Europe to convince medical professionals that not informing of a cancer diagnosis could in fact cause more suffering than knowing about the diagnosis might cause (Cassileth, Zupkis, Sutton-Smith, & March, 1980; Novack et al., 1979). In many Western countries, cancer has become a partially explainable and treatable disease and mythical fears have now shifted to genetic diseases. These are, like cancer disease earlier, associated with fatality, lack of treatment and stigmatization. Telling somebody about a genetic predisposition to untreatable diseases or hereditary cancer revives traditional paternalistic concerns. Typically, as previously, the majority of oncologists (Oken, 1961), geneticists and medical professionals seem to be more fearful of negative consequences than are individuals who are at risk for genetic disease (Thomassen et al., 1993; Tibben et al., 1993). A majority (Wertz, 1994) or at least a significant minority (Bradbury et al., 2008) of genetics patients would have adolescent children tested for adult-onset diseases. In another study, researchers reported irritation and anger among parents who were told that the research team "simply would not test their children" before the age of majority (Lynch et al., 1997). The arguments used for other types of genetic testing during childhood apply also to predictive testing for adult-onset diseases: according to a classical rule in medical ethics, patients should be given an important role in decisions where health professionals disagree. Parents and their children

might be in a better position than health-care professionals to most adequately judge the benefits and harms of testing an individual child (Cohen, 1998; Robertson & Savulescu, 2001).

Although it is appropriate for physicians and geneticists to advice against predictive testing of minors, it is ethically justified to allow for exceptions on a case-by-case basis. Indeed it is ethically difficult to defend refusal of such testing unless there is considerable evidence that testing will harm the child. However, before allowing the test, adolescents and parents should be informed about the psychosocial risks and benefits (see Table 4). Interestingly, results of most recent studies indicate that,

Table 4. Psychosocial Risks and Benefits of Genetic Testing of Children for Adult-Onset Diseases

- *Benefit of informing children about genetic predispositions or about results of the testing done during childhood*: Knowing about a disease predisposition and sharing knowledge with other family members alleviates emotional isolation. If it is judged adequate and beneficial to inform children that they are at risk for an adult-onset disease that exists in the family, the consequences of testing, i.e. of the wish to know whether a child actually carries the genetic mutation, could be considered similar (Malpas, 2006)
- *Psychological benefit of testing*: Uncertainty is reduced. For persons at risk for Huntington's disease who desire to know, receiving bad news may be psychologically less deleterious than uncertainty (Lerman et al., 1997; Lynch et al., 1997; Wiggins et al., 1992). According to Wiggins et al. (1992), the reduction of uncertainty in persons who wanted to know was associated with a decrease in depression scores in non-carriers and carriers. Both non-carriers and carriers in unaffected subjects showed consistent reductions in distress and impairment, while those not tested showed small increases or no change (Lerman et al., 1997). A clear disadvantage of postponing genetic testing to the age of majority for adolescents knowing themselves being at a 50% risk of carrying a HD or a *BRCA1* mutation are several years of uncertainty. Therefore, some parents consider it irresponsible not to use testing to remove their children's doubt and anxiety (Arribas-Ayllon, Sarangi, & Clarke, 2008)
- *Benefits for the pursuit of career and life plans:* For a rational person wishing to pursue rational life plans, knowing whether she is carrying a mutation predisposing to an adult-onset disease can be a major benefit. Important decisions about career and life orientation are often made early in life (choice of an instrument to play, choice of school type), or at least between the ages of 14 and 17 years. In many European countries, the choice of the type of baccalaureate (for example humanities or science oriented) is a decision about future job orientation as well as the decision to quit school after the obligatory 9 years in order to start an apprenticeship in a special area. A minor may also wish to decide about becoming pregnant. A female adolescent who is a *BRCA1* mutation carrier might decide against a long university education in order to have children early and pursue a university career after having had bilateral mastectomy and oophorectomy
- *Benefits of granting choice and/or autonomy to children and adolescents:* Granting decision autonomy to children and adolescents has proven to be beneficial. "Choice results in increased perceived value of the chosen object" (Melton, 1983b, p. 31). When children or adolescents are given the freedom to decide, "they will be more likely to follow through on that choice" (Melton, 1983a). Increasing children's participation in decision making related to treatment of a chronic illness improves treatment compliance, according to research studies (Grodin & Alpert, 1983; Lewis, 1983; Weithorn, 1983). Permitting minors' involvement in decisions affecting their own welfare has been claimed to be in the child's best interest since increased autonomy heightens children's sense of "personal causation", i.e. their experience of being in control (Weithorn, 1983). The experience of being in control and having a sense of mastery over what happens to one has been

(Continued)

Table 4. *(Continued)*

suggested as directly related to a person's adaptive and healthy psychological functioning (ibid., p. 241). Taking children's choices concerning genetic testing seriously increases their sense of themselves as active and responsible participants in questions related to their own psychological and physical health rather than as powerless victims of adults and genes. Even authors against the genetic testing of children admit that "granting choice and control with respect to genetic testing. . .may be of value to the adolescent's self-esteem and hence his or her coping strategies" (Clarke & Flinter, 1996, p. 166)

- *Psychological harm of testing*: Studies about the psychological effects of genetic testing for the Huntington's disease mutation showed few negative consequences if testing had been requested by the person at risk. Only a small minority (5%) of all persons tested reported regretting their decision (Codori & Brandt, 1994). Those identified as carriers did not show increases in depression and functional impairment. It is not clear whether children and adolescents are more vulnerable than are adults in regard to the information to be carrier of a mutation predisposing to an adult-onset disease. If they are more vulnerable, this can be used as an argument for both sides. Knowing that one carries a mutation associated with a high lifetime risk of cancer or HD can certainly diminish the already unstable self-esteem of an adolescent. On the other hand, the uncertainty of a 50% risk of carrying the mutation could be even more difficult to bear for an adolescent. In addition, the difference in regard to self-esteem between knowing to be a member of a family with a hereditary disease predisposition and having a 50% risk for cancer or HD and the confirmation of an increased risk might not be substantial
- *Adverse social and educational consequences*: The possibility of adverse social and educational consequences for some adolescents has been pointed out by those against their genetic testing (Clarke & Flinter, 1996). In the case of population screening for *BRCA1* mutations where a previously "healthy" adolescent is identified after having been tested as being at high risk of cancer some years later in her life, the danger of such negative consequences is obvious. This is not the same for children from families with several cases of hereditary cancer due to an identified mutation. Being from such a family, children are already at high risk of adverse social and educational consequences. Psychologists in contact with families at risk for Huntington's disease have observed that consciously or unconsciously families differentiate between children believed to carry the mutation and those supposed not to carry it. The former have been discriminated in respect to psychological and educational questions without any genetic test having been carried out (Kessler, 1993, 1994). In the worst case, stigmatization and discrimination by the family cannot be avoided. However, competent adolescents could be protected by granting confidentiality of the results if stigmatization and discrimination are feared. Confidentiality about genetic testing can be justified in adolescents. Test results concerning a hereditary disease may influence their sexual behaviour. In other medical areas related to sexual behaviour (contraception, sexually transmitted diseases), adolescents have already been given the right to confidentiality. If it is difficult to maintain confidentiality, this could speak in favour of testing only older adolescents since possible devastating educational and social consequences are limited to a few years
- *Risk assessment from a less pessimistic point of view*: The pessimistic evaluation that "children who are tested may face limited futures and that testing may result in damage to the child's self-esteem" has been criticized on the grounds that these arguments do not stand up to critical evaluation (Malpas, 2008). The risk for stigmatization and educational and social discrimination because of a predisposition to hereditary breast and ovarian cancer could be less important as often feared. Breast cancer is a very common disease and no longer implies a stigmatization in Western culture, especially since breast cancer is curable in a high number of cases. Hence, the rational basis of educational and social discrimination is rather small
- *Financial risks:* The debate about the right of insurers and employers to use genetic information in order to discriminate against persons at risk for disease has led to legislative efforts in the United States to prevent such adverse consequences (Borchelt, 2008). Gene carriers are at risk of facing more important financial burdens than are

Table 4. *(Continued)*

non-carriers, although the fact of being at 50% risk is often enough for risking discrimination and therefore a gene test could be beneficial for half of the children at risk who are non-carriers
– *Loss of privacy:* If parents are informed about the test results of their children, the latter will never be able later to decide freely whether they want their patients to know or not. As shown above, for adolescents this problem could be resolved by granting confidentiality
– *Loss of autonomy:* The right of individuals to make their own decisions about testing as autonomous adults is said to be compromised if the decision is taken during childhood. The assumption is that individuals have sufficient decisional autonomy from the age of 18. Those who argue against decisional autonomy of minors claim that lifetime autonomy should be given preference over present-time autonomy. From an empirical point of view, it is evident that great variability exists between different persons. Some 11-year-old children are more mature than some 19-year-old adults. In addition, the lifetime autonomy of an individual is threatened only if evidence suggests a substantial risk for a change in attitudes with the adult regretting the decision made as a child or an adolescent. Concerning HD, empirical studies have shown that only a very small proportion of persons having chosen to have a gene test have regretted their decision

independently from any testing, informing children about their mother's hereditary cancer can engender children's cancer worry (Tercyak et al., 2001; Tercyak, Peshkin, Streisand, & Lerman, 2001). On the other hand, given the widespread discussion in the mass media of genetic diseases and genetic testing, it might not be a realistic option to hide the information of a hereditary cancer predisposition to an adolescent in a family with several cases of breast and/or ovarian cancer and perhaps some relatives having undergone mastectomy or oophorectomy. If in such cases, competent adolescents ask themselves repeatedly for testing, it could be judged ethically inappropriate to deny testing, especially since 50% of these children are supposed to receive a test result indicating that they have not inherited the mutation and could be relieved from most of their anxiety (the average 10% lifetime risk of breast cancer of any other women in Western societies persists). "Survivor guilt" has been mentioned as an argument against testing on the grounds that even those family members who have not inherited the mutation will suffer from negative psychological reactions in spite of the absence of the mutation. This term does, however, not necessarily adequately depict the feelings of non-mutation-carriers. Overall, 1 year following disclosure, non-carriers described relief and personal growth and reported that relationships with other relatives were closer (Claes et al., 2005; Valverde, 2006).

In the ethical discourse about decisional autonomy and best interest of the child, there is often not enough room for the complex ways in which physicians, parents and children are influenced by what is culturally or ethically appropriate. All persons concerned have to struggle with conceived ideas of self-responsibility and other responsibilities concerning taking a test themselves, informing other family members about genetic risk and making reproductive choices. Although non-directive counselling is the "Mantra" of medical genetics, one wonders whether this ideal can be achieved in current Western societies. The ethical imperative enshrined in ubiquitous guidelines is that individuals have the right to know and the

right not to know. However, studies have also shown that most individuals, women more than men, feel ethically responsible to take reproductive decisions with the aim to avoid the birth of an affected child (Elger, 2005; Elger & Harding, 2003; Elger & Harding, 2006). Paradoxically, it could be this pressure towards responsible behaviour which interferes with the freedom to seek knowledge and relief from uncertainty; at present, once the genetic predisposition is confirmed, choices are limited due to the felt pressure of ethical responsibility. It could be ethically more justified for geneticists and physicians to support the wish of parents and childrens to know while informing and reassuring them that they have a right to have children and to make reproductive and life decisions without feeling any type of eugenic pressure.

Conflicting Interests of Parents and Their Children

Parents' child planning may depend on the genetic predisposition of existing children. Couples who have one or two affected children might want to have another child. They might renounce another pregnancy if they know that at least one of their children has not inherited the mutation. Framed in terms of autonomy and responsibility, a conflict exists between preserving the autonomy of the existing children until the age of majority and the right of parents to make autonomous and responsible decisions (Duncan & Delatycki, 2006; Robertson & Savulescu, 2001). Although young children who will have to bear the consequences of genetic testing cannot give informed consent, it might not be justified in all cases to try to dissuade parents from testing (Sarangi & Clarke, 2002; WIlfond & Ross, 2008). Limits to parental autonomy need to be recognized and are justified if parental decisions imply significant harm to their children. The recommendation that children should not be tested for adult-onset diseases does not become invalid if it is accepted that exceptions are ethically justified on a case-by-case basis, balancing best interests of all family members involved.

Frequently parents support the testing of their children and criticize the decision of geneticists to postpone testing. If the request to test comes from a competent adolescent, it is important to ensure that the adolescent's wish is autonomous and independent. The test should not be carried out if the adolescent is influenced by parental pressure.

What should be done if parents are opposed to the wish of their competent adolescent child to be tested before the age of 18 years? The right of any person to have a genetic test could be limited if autonomy rights or important interests of other persons are in danger. L. F. Ross claims that parents have the right to pursue family goals which may compete and conflict with the goals of particular members (Ross, 1997). A family goal might be to hide from the children the existence of an adult-onset or other genetic disease in the family. However, at least children who reach reproductive age should be granted a right to know about the hereditary disease. Once adolescents know about their genetic predisposition, which could be important interests for the parents to prevent their children from undergoing the test? Parents might wish, in the best interest of

other younger children, to avoid creating a difference between their children in terms of risk. However, this difference is inevitable a few years later when these adolescents reach majority. Older siblings might have already used their right to be tested at the age of 18. Parents may want to keep their children from taking the test because they do not want to know themselves if they have not been tested and are asymptomatic. The right not to know of the parents could be preserved if they are not informed about the test results of their competent adolescent child.

FUTURE DEVELOPMENTS AND CONCLUSIONS

The analysis of the ethical, legal and social issues in the genetic testing of minors has shown that over the past 20 years, recommendations against such testing did not change significantly. Advances in available testing and extension of newborn screening have stirred additional controversy. It became clear that some ethical options do not exist anymore, for example if newborn screening reveals not only homozygous babies but also heterozygous carriers. Since the information that a newborn is a carrier cannot be undone and there is no realistic option of noting this information, but not telling parents, preserving the benefits of newborn screening inevitable implies accepting carrier testing for some newborns. Surprisingly, studies about consequences of testing minors have been rare during the past years, although most publications insist that they are important to guide ethical and legal decisions. The reason for the dearth of studies might be the recognition that consequences are difficult to predict because they vary widely between different individuals, families and social circumstances. Other likely reasons are that testing of children is rare and that geneticists who perform it are reluctant to publish on this issue since their attitude is contrary to existing guidelines (Duncan & Delatycki, 2006). This effect of guidelines is not in the interest of children. The reality is that some children are tested for adult-onset diseases and that nothing is known about whether the testing was justified and what the consequences were. Given the persisting ethical, legal and social stakes, it would be better, if children are tested, to do it always and only in a research context to be able to gather more data. Hence, parents and adolescents who request testing after appropriate information should not be refused this possibility. Instead, the importance to participate in research should be explained to them. It should be noted that research could also offer a protective framework to diagnose adverse effects of testing early and to provide psychological and social support. Similarly, if geneticists and physicians refuse testing, the ethical imperative for the future should be to evaluate consequences of these refusals.

At present it is too early to judge whether the new legislative efforts in the United States (Borchelt, 2008) will change the risks concerning discrimination by insurers and employers. The United States has just passed the Genetic Information Nondiscrimination Act (GINA), but there are conflicting predictions about how effective that Act will actually be. Since, for most Americans who have insurance, their health insurance is tied to

their employment, they are very vulnerable to genetic discrimination – one could lose both one's employment and one's health coverage.

Ethical, legal and social issues in genetic testing of children vary considerably in relation to different hereditary diseases. Since more and more mutations defining genetic predispositions are being discovered, judging the benefit–harm ratio is difficult not only because of significant differences between individual children, families and social situations but also due to individual aspects of different diseases which occasion distinct challenges concerning coping strategies.

In conclusion, taking the decision to test or not to test a child will never be a decision where one enters demographic and sociological variables in a computer program which calculates a score of a benefit–harm ratio. These decisions will always remain individual choices and responsibilities. The process by which a decision is reached and the way it is later accompanied (follow-up and help offered) may be more important than the content of the decision – for or against testing – itself.

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Guidelines and Policies on Genetic Testing in Children and Families

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Rapid advances in genomic-based sciences are facilitating the collection of a burgeoning amount of knowledge about the role that genomic factors play in human disease. The resulting body of knowledge provides hope for more effective treatments and eventually the prevention of diseases and disorders affecting children, adults, and families (Feero, Guttmacher, & Collins, 2008; Guttmacher & Collins, 2005). However, this knowledge and technology could be used inappropriately, resulting in harm to the medical, psychological, and social well-being of those pursuing testing (Hudson, Javitt, Burke, & Byers, 2007; Robertson, 2003). The rapidly increasing breadth and availability of genomic tests are leading to heightened concerns about their application in clinical settings, public health, and outside of the health-care setting, through direct-to-consumer (DTC) marketing (Hudson et al., 2007; Javitt, Stanley, & Hudson, 2004). These concerns are particularly relevant for genetic and genomic testing of children, due to complicating factors such as consent for testing, protection of children's autonomy, and the implications of learning genetic risk information early in life (Wilfond & Ross, 2008). Such concerns have led to the development of a number of position statements and clinical practice

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guidelines intended to aid genetic service providers, individuals, and families when considering the appropriateness of genetic testing for children. Concerns have also extended to the oversight and regulations of laboratories conducting genetic testing resulting in assessment at the federal level to ensure the quality and efficacy of testing being conducted.

The purpose of this chapter is to gain insight into the existing research, guidelines, and policies that influence the use of genetic and genomic testing in children and their families. To accomplish this, this chapter will present a review of existing position statements and practice guidelines, federal and state support and legislation, research on pediatric genetic testing, and committee and task force recommendations on genetic testing. The roles of federal agencies that influence policy perspectives, including the regulatory oversight of laboratories conducting genetic testing, will be explored. Case-based scenarios are included to highlight impending challenges posed by genomic technology as it relates to testing during childhood.

BACKGROUND

Historically, genetic testing has been cast as different than other forms of medical testing due to the perceived potential for social, psychological, medical, and legal harms to the person undergoing testing. Genetic testing may also provide information for biological family members, based on the principles of Mendelian inheritance and other complex forms of inheritance more recently described. These potential harms extend to biological family members, who may or may not be interested in receiving genetic risk information. The identification of persons at increased risks to develop disease has held the potential for discrimination in health, life, and disability insurance. The potential for misuse of genetic information has also arisen within the context of current and future employment opportunities. Such harms have led professionals, consumers, and legislators to advocate for policies, protocols, and legislation that comprehensively protect consumers and their families before and after the receipt of genetic information (Task Force on Genetic Testing, 1997).

Genetic testing that is considered or pursued during childhood has the potential to cause additional harms, as children often cannot make truly informed decisions on their own and rely on adults (e.g., parents and health professionals) to make or facilitate such a decision on their behalf. This situation has generated significant concern about the psychological and social impact of such testing during childhood. Nevertheless, pediatric genetic testing is conducted under several situations. Tables 1–4 provides a categorical listing of the types of genetic testing that are possible during childhood along with the intended uses of such testing, selected disease-specific examples, and our comments regarding current practice and policy perspectives. The following sections will elaborate on each of the categories and provide case scenarios to familiarize the reader with their current clinical applications and challenges. A case scenario is also presented to facilitate consideration of pediatric testing for common complex health risks.

Table 1. Categories of Genetic Testing Potentially Conducted During Childhood or Adolescence; Diagnostic Testing

Category of Testing	Purpose of Testing	Examples of Diseases	Comments
Diagnostic testing Child/adolescent presents with symptoms, medical/developmental problems, or uncommon features; genetic condition is suspected as the cause	Confirm/rule out suspected diagnosis Guide medical management	Hundreds of genetic tests exist; Selected examples: • Neuromuscular disease Duchenne muscular dystrophy Spinal muscular trophy Friedreich ataxia • Chromosomal disorders Down syndrome Klinefelter syndrome Turner syndrome Trisomy 18/trisomy 13 • Neurodevelopmental disorders Fragile X syndrome Smith–Magenis syndrome Neurofibromatosis Prader–Willi syndrome Williams syndrome • Cancer syndromes Multiple endocrine neoplasia (MEN) Li–Fraumeni syndrome Ataxia telangiectasia Cowden syndrome • Connective tissue disorders Marfan syndrome Stickler syndrome • Multiple system disorders 22q deletion syndrome Immune disorders • Severe combined immune deficiency	Physician directed Parental consent necessary with assent of children over 7 Testing must be conducted in CLIA approved lab

Genetic Testing in Children for Diagnostic Purposes and Medical Management

Despite the complexities involved, genetic testing for the purpose of diagnosis and medical management in children and adults who demonstrate clinical symptoms has long been an accepted practice (Table 1, Panel A). This testing has typically been conducted within the confines of clinical genetics programs, which provide comprehensive education and counseling prior to and after testing (National Society of Genetic Counselors, 2006). Even in those settings, assuring accurate knowledge and implementing appropriate health behaviors can present challenges. However, the benefits gained through molecular confirmation (genetic testing) of a suspected diagnosis may provide significant guidance for

the medical care and management of a child and family. From a clinical perspective, the benefits of genetic testing in this type of situation are believed to outweigh the potential risks and harms associated with pediatric genetic testing in other contexts. Therefore, professional practice guidelines recommend genetic testing when a child presents with symptoms suggestive of a genetic disorder for which a causative gene(s) is known (The American Society of Human Genetics, 1995).

Figure 1 provides a family medical history, depicted in pedigree format, of a couple that considered genetic testing for their 8-month-old daughter. Their daughter developed progressive muscle weakness beginning at 6 months of age, accompanied by poor weight gain and scoliosis (curvature of the spine). Case Scenario 1 describes the benefits and challenges of diagnostic genetic testing. Families face a breadth of issues when confronted with childhood-onset disease with a genetic basis. Such case studies serve to inform practice and develop policy.

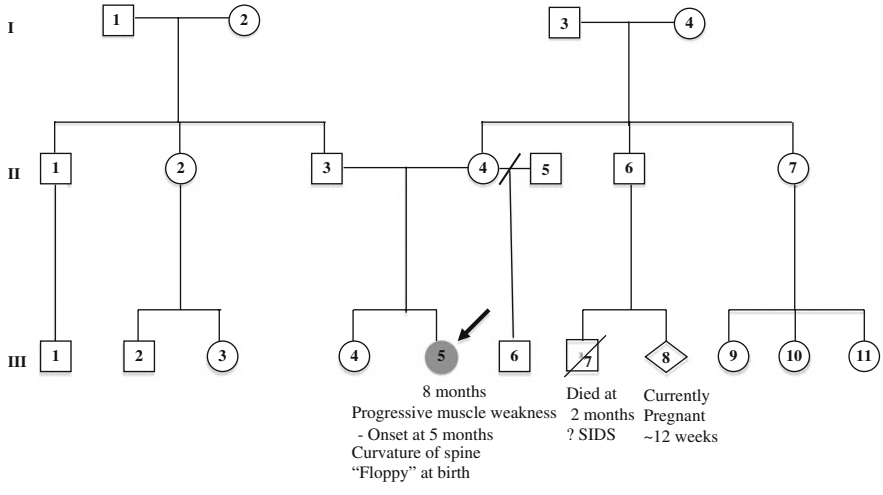

Figure 1. Case-based pedigree.

Genetic Assessment Through Newborn Screening

In the USA, newborn screening (NBS) is a state-based public health program that began over 40 years ago (Table 2, Panel B). States and territories mandate screening of all newborns for selected disorders that may not be otherwise detected before disability or death occurs. Although the list of mandated disorders varies from state to state, it is nationally recognized as a model of public health-based population genetic screening (The American College of Medical Genetics, 2006). Infants with these diseases often appear normal at birth. Compliance with the recommended medical management results in saved lives, improved prognosis, or, in some cases, avoidance of many expected complications.

Generally, testing in NBS does not directly assess disease-causing genes. Rather, NBS assesses biochemically related gene products through a blood sample collected soon after birth. The process used to inform

Table 2. Categories of Genetic Testing Potentially Conducted During Childhood or Adolescence; Newborn Screening

Category of Testing	Purpose of Testing	Examples of Diseases Where Such Testing Is Utilized	Comments

Newborn screening (NBS)
All babies born within a US state or territory undergo screening
	Identify newborns prior to the onset of symptoms allowing disease management which may prevent or significantly reduce the impact of the disease	• Diseases screened vary by State and US Territory.
		• 29 diseases proposed for mandated inclusion by all states (ACMG)
		• 25 additional conditions identified for consideration due to:
		  • part of differential diagnosis of condition in core panel of 29
		  • clinically significant but lack efficacious treatment
			• States mandate testing
			• Parents may opt out
			• Testing must be conducted in CLIA approved lab

parents of NBS varies from state to state; frequently, parents are provided with written materials at the time of birth. Parental refusal of NBS can occur under certain situations including religious objections.

Four disorders, including phenylketonuria (PKU), congenital hypothyroidism (CH), galactosemia (GAL), and sickle cell disease, are included in every state's NBS program (http://genes-r-us.uthscsa.edu/nbsdisorders.pdf). PKU is a rare, inherited metabolic disease affecting about 1 in 10,000 live births and provides a classic example of disorders typically included in NBS programs. In individuals affected by PKU, the enzyme phenylalanine builds up in the body and may result in mental retardation, other neurological problems, and a shortened life span. When a very strict, protein-free diet is begun within the first few weeks of life, many of the medical problems can be lessened or avoided altogether with expectation of a normal life span. Every state currently requires newborn screening for PKU.

In contrast to PKU, SMA (see Case Scenario 1) is not tested for during NBS, since there is no conclusive evidence that therapies will prevent or delay its onset. Despite this, families of children with SMA are lobbying to include it within NBS programs. These parents believe that early diagnosis of SMA and subsequent early medical intervention (e.g., nutrition, physical therapy, and respiratory care) will extend the life span of babies with SMA, improve quality of life, and help families coping with the problems facing their affected family member. They also argue that early diagnosis would eliminate the pain and cost of unnecessary testing that would otherwise take place in attempting to diagnose an affected child. Earlier diagnosis

could also provide parents with earlier genetic counseling, which would allow them to evaluate their reproductive plans and options prior to a future pregnancy.

Carrier Screening During Childhood and Within Families

Carrier screening refers to genetic assessment of individuals who do not show symptoms or characteristics of the disease in question (Table 3, Panel C). These individuals may be at risk of carrying a genetic mutation and having children with the disease. When considering autosomal recessive conditions, a carrier would possess one copy of a disease-causing gene and one normally functioning copy with no symptoms of the disease expressed. Carriers of X-linked diseases are notably females who possess one X chromosome with a single copy of a disease-causing gene mutation and a second X chromosome that has a normally functioning copy. Since females have two X chromosomes, they typically show either no signs of disease or milder signs than affected males. Carrier screening is most often undertaken to clarify reproductive risks. Statements developed by numerous professional groups generally support the use of carrier screening in adults (Prior, 2008). However, carrier screening during childhood is discouraged due to the potential for social and psychological harms in the absence of any direct medical benefit. Case Scenario 2 illustrates some of the challenging issues carrier testing presents to adults and children.

Table 3. Categories of Genetic Testing Potentially Conducted During Childhood or Adolescence; Carrier Screening

Category of Testing	Purpose of Testing	Examples of Diseases Where Such Testing Could Be Utilized	Comments
Carrier screening Symptoms are not present in person considering testing Person considering testing is potentially at risk to have a child with an autosomal recessive, x-linked, or mitochondrial disease, or a chromosome-based disorder	To identify persons at increased risk to have child affected with the disease in question	Tay–Sachs disease X-linked severe combined immune deficiency Sickle cell disease Hemophilia Cystic fibrosis Duchenne muscular dystrophy Spinal muscular atrophy Fragile X syndrome Chromosomal translocations	Generally discouraged during childhood in the absence of medical benefits[a]; concerns regarding psychosocial risks suspected to outweigh potential benefits Some research reports interest in carrier testing by parents Assent by child appropriate, if testing approved Testing must be conducted in CLIA approved lab

[a]American College of Medical Genetics, American Society of Human Genetics, National Society of Genetic Counselors, American Society of Clinical Oncology.

Presymptomatic and Susceptibility Testing for Inherited Disease and Disorders

The introduction of presymptomatic and susceptibility testing in the early to mid-1990s brought a new wave of challenges in providing risk information pertaining to inherited diseases, some with onset in childhood and others with onset in adulthood (Table 4, Panel D). In some cases, preventive or early detection options exist in childhood, and in those cases presymptomatic or susceptibility genetic testing is routinely offered to children with parental consent along with comprehensive education and counseling (Case Scenario 3). However, the offer of presymptomatic or susceptibility genetic testing to children for diseases with onset in adulthood and no known preventive options available during childhood has been an area of considerable debate (Case Scenario 4). Preventive options for adult-onset conditions are typically not available in childhood. However, some parents have expressed interest in having children tested to determine their risk for the disease in question. In the absence of sufficient empirical data on the psychological and social outcomes of pediatric genetic testing for adult-onset diseases, greater weight has, historically, been given

Table 4. Categories of Genetic Testing Potentially Conducted During Childhood or Adolescence; Presymptomatic and Susceptibility Testing

Category of Testing	Purpose of Testing	Examples of Diseases Where Such Testing Is or Could Be Utilized	Comments
Presymptomatic/ susceptibility testing for inherited disorders:	To identify persons who are at increased risk to develop diseases		Parental consent & child assent is necessary Testing must be conducted in CLIA approved lab
• Onset potentially in childhood or adolescence	Identify gene carriers to initiate treatment/medical screening to reduce risks, prevent disease, or improve prognosis	Familial adenomatous polyposis Multiple endocrine neoplasia (MEN) Li–Fraumeni syndrome	
• Onset in adulthood	Suggested benefits include improved psychological and social adaptation to carrier status prior to adulthood	Huntington's disease Hereditary cancer syndromes • Breast and ovarian • Lynch syndrome (colorectal) Alzheimer's disease Parkinson disease	Generally discouraged during childhood in the absence of medical benefits[a]; concerns regarding psychosocial risks suspected to outweigh potential benefits

[a]American College of Medical Genetics, American Society of Human Genetics, National Society of Genetic Counselors, American Society of Clinical Oncology.

to the potential risks of such testing. Therefore, presymptomatic or susceptibility genetic testing for adult-onset conditions has been reserved as an option for adults, preserving the rights of a child to make their own informed decision at a later age, prior to the advent of medical screening or intervention to reduce disease risks.

Genomic Testing for Common, Complex Disorders: Considerations for the Future

Limited research exists on the perspectives of, interest in, and psychological outcomes of genetic testing in children while no research exists on genomic testing. Some evidence suggests that children and parents do not agree on the purpose or ideal timing of genetic testing (James, Holtzman, & Hadley, 2003), while other research finds that parents and children present similar perspectives on genetic testing (McConkie-Rosell, personal communication). These differences may reflect the varying experiences of families in which children are affected with diseases that present significantly different challenges (e.g., cognitive challenges, dysmorphic features, medical issues or combinations therein). These issues will become even more complicated as genomic testing potentially expands to include markers for complex diseases (e.g., cancer, heart disease, diabetes), psychiatric conditions (e.g., bipolar disorder, schizophrenia), or, eventually, other complex phenotypes (e.g., intelligence, personality, psychiatric profile, muscle mass, obesity, susceptibility to addictive behaviors). In certain situations, the benefits of genomic testing seemingly outweigh the potential risks, such as using genomic knowledge when prescribing medications.[1] However, the increasing number and complexity of genomic tests will likely raise the potential for psychological and social harms to children, their families, and society. Likewise, the wide range of issues presented by the breadth of diseases or conditions under study (e.g., adult versus childhood onset, availability and efficacy of medical treatment, availability and efficacy of preventive options) will provide significant challenges to the development of guidelines or policies related to genomic testing.

There is growing pressure to reconsider current policy perspectives on pediatric genetic testing (Wilfond & Ross, 2008) as genomic data are rapidly accumulating for common diseases with complex genomic/environmental interactions. Eventually, evidence-based prevention options may be available, which will reduce risks based on the specific underlying biochemical or genetic markers associated with the disease or phenotype. However, at this point in time, individuals with a genetic marker that increases medical risks do not have preventive options specific to the genetic cause of their risk. Instead, treatment and preventive approaches developed for the general population may be utilized, which

[1]Pharmacogenomics involves selecting medications based on an individual's genetic makeup that provide the greatest efficacy, while balancing the adverse effects of the drug.

may or may not be effective in reducing the identified risk. Case Scenario 5 provides an example of the challenges presented to families by the availability of genomic testing in the absence of evidence-based prevention options.

National and international discussions about genetic testing, including the potential impact of pediatric genetic testing, began in earnest in 1994. Since then, numerous committees, task forces, and federal agencies have debated the issues related to genetic testing of children, generated multiple guidelines and position statements, and recommended different courses of action. Unfortunately, these efforts have limited empirical research on genetic testing of children. This, in turn, limits the availability of research-based evidence to deliberations and recommendations. To inform thoughts and discussion on policy, it seems prudent to begin with a review of existing research on pediatric genetic testing.

RESEARCH AND EMPIRICAL LITERATURE ON PEDIATRIC GENETIC TESTING

Examining national policy perspectives on pediatric genetic testing necessarily requires the consideration of the research and empirical literature on the topic. Although predictive genetic testing of children has been debated since it became a possibility, there is little empirical evidence on genetic testing of children for adult-onset conditions (Duncan & Delatycki, 2006). What limited research exists has examined reasons for and against genetic testing, as well as the outcomes of genetic testing of minors.

One important consideration in determining whether minors should undergo genetic testing is whether the proposed testing provides any medical benefit. In the context of proven medical benefits, genetic testing of children for late-onset conditions generally occurs (Borry, Goffin, Nys, & Dierickx, 2008; Campbell & Ross, 2003). However, genetic testing of minors for adult-onset conditions when no medical benefit can be determined is less accepted (Borry et al., 2008; Campbell & Ross, 2003; Duncan, Savulescu, Gillam, Williamson, & Delatycki, 2005). A systematic review of relevant position papers and guidelines demonstrated the lack of consensus on the topic (Borry et al., 2008).

Reasons for Genetic Testing of Minors

Parents frequently request genetic testing of their minor children; five guidelines included in a systematic review do recommend leaving testing decisions up to parents (Borry, Fryns, Schotsmans, & Dierickx, 2006). A study of health-care providers in the USA, UK, and Australia found that immature young people (younger than 14) were most often tested for adult-onset conditions because the parents requested it (Duncan et al., 2005). A US-based focus-group study found that parents viewed themselves as the final arbiter of whether their child should have genetic testing (Campbell & Friedman Ross, 2005). Many providers are willing to accede

to parents' requests for genetic tests, even if they do not believe the tests are clinically useful, and they would not use the tests on their own children (Campbell & Ross, 2003). Requests from the young person and/or parents were more common in genetic testing of mature young people (older than 14). Mature young people were most often seeking to resolve uncertainty, as well as plan for the future (Duncan et al., 2005; James et al., 2003). Parents also requested genetic testing in the belief that they could do something to prevent or treat untreatable conditions (Campbell & Friedman Ross, 2005).

Reasons for Deferring Genetic Testing of Children

Over half of the providers in the study conducted by Duncan and colleagues had refused to perform a predictive genetic test on multiple occasions. The most common reasons for deferring testing included protecting the young person's autonomy, no medical benefit, the possibility of harm, policy, counseling used to resolve the issue, and privacy (Duncan et al., 2005). Parents also expressed concerns about confidentiality and discrimination resulting from genetic testing (Campbell & Friedman Ross, 2005).

Outcomes of Genetic Testing in Children

Two studies found that children tested for FAP (Codori et al., 2003; Michie, Bobrow, & Marteau, 2001) did not demonstrate clinically significant psychological distress after testing nor did their parents experience clinically significant long-term distress after their children were tested (Codori et al., 2003). These studies detected some concerning findings in children who tested positive for FAP. In one study, mutation-positive children with mutation-positive siblings demonstrated higher depression scores at long-term follow-up, compared to baseline and 3-month follow-up, and compared to mutation-negative children with mutation-negative siblings (Codori et al., 2003). In another study, children who tested positive for the genetic mutation were more distressed about FAP in their family and were more anxious than children who tested negative (Michie et al., 2001).

A study of providers found that some parents who requested genetic testing of immature children (younger than 14) for adult-onset conditions experienced distress and anxiety. Parents were distressed about having the information, and anxious about when and how to tell the child about the test results (Duncan et al., 2005).

Young people who had genetic testing later described the potential harms and benefits of testing and the testing process. Harms and benefits were not intuitively split according to mutation status (Duncan et al., 2007). Young people also highlighted the importance of placing genetic test results into a broader context – to enable them to understand and adapt to the information that they are gaining through genetic testing (Duncan et al., 2007).

Attitudes Toward Genetic Testing

Children and adolescents are interested in having genetic testing (Bernhardt, Tambor, Fraser, Wissow, & Geller, 2003; James et al., 2003), and their parents tend to agree (Bernhardt et al., 2003). Children examined potential issues related to genetic research, but focused on the research project itself, while parents focused on issues related to the genetic test (Bernhardt et al., 2003). In another study (James et al., 2003), sisters of males with chronic granulomatous disease (CGD) expressed interest in carrier testing, a sentiment echoed by their parents. However, the girls' interest was tied to a time when the information might be of relevance to future planning such as when they were becoming sexually active or planning a family. Their timing of when testing might be appropriate was notably later than their parents who felt, in some cases, testing should be done as soon as possible.

Most articles addressing the issue of pediatric genetic testing have focused on single-gene disorders; one exception examines adolescents' interest in genetic susceptibility testing for nicotine addiction (Tercyak, Peshkin, Wine, & Walker, 2006). The majority of adolescents expressed an interest in this testing (62%). Those who were interested in testing did not identify intentions to change behaviors, while those who thought testing was useful were more likely to mention the potential behavioral benefits of testing (Tercyak et al., 2006).

There is a dearth of empirical research addressing predictive or presymptomatic genetic testing of children. Few authors have included at-risk young people in their study samples, yet having such data would inform discussions, positions statements, practice guidelines, and, inevitably, decisions regarding policy. In its absence, truly informed decisions are not possible, which may lead to ill-informed oversight.

US TASK FORCES AND COMMITTEES ASSESSING GENETIC TESTING

National Institutes of Health – Department of Energy Working Group on Ethical, Legal, and Social Implications of Human Genome Research

The Ethical, Legal, and Social Implications (ELSI) Working Group (NIH ELSI Program, 1997) was established in 1989 by the Program Advisory Committee on the Human Genome to explore and propose options for the development of the ELSI component of the Human Genome Project. From 1989 to 1997, the Working Group provided overall guidance to the National Human Genome Research Institute (NHGRI) and Department of Energy (DOE) ELSI programs, facilitated a number of early policy discussions, and participated in the development of a number of policy options and recommendations related to these issues.

The Working Group also formed two task forces aimed at analyzing and developing recommendations on (1) genetic information and

health insurance and (2) genetic testing. The final report of the Task Force on Genetic Information and Insurance was published in 1994 (Genetic Information and Health Insurance Report of the Task Force on Genetic Information and Insurance; http://www.genome.gov/10001755). The Task Force's recommendations on genetic testing (detailed below) have been utilized in a number of legislative proposals related to health-care reform.

While the Working Group's efforts were broadly focused on genetic testing in general, i.e., not specific to children, the Group did produce a statement on population screening for cystic fibrosis (Program, 1990). At that time, the Working Group discouraged (1) newborn screening primarily to detect heterozygous carriers and (2) carrier screening programs directed at children not yet of reproductive age.

Institute of Medicine

In 1994, the National Academy of Sciences and its charter, the Institute of Medicine (IOM) produced what is arguably one of the most influential and comprehensive documents on genetic testing. The committee's goal was to address the issues surrounding the assessment of genetic risk and genetic testing. The committee's findings and recommendations were published in book form (Andrews, Fullarton, Holtzman, & Motulsky, 1994). At that time, the multidisciplinary committee noted that no single voice had the authority to make policy recommendations pertaining to genetic risk assessment and testing. However, the committee's proceedings and recommendations were intended to serve as the basis for future discussions and policy regarding genetic testing. The committee stressed that the many health and social policy issues raised by genetic testing would not necessarily have a single or unambiguous solution. Although the committee recognized that the reduction of genetic disease might be considered the primary goal of work in this arena, it ultimately promoted the importance of autonomous decision making by individuals and families even if genetic disease might be the outcome.

In addition to these more general recommendations, the IOM report is one of the few to address genetic testing in children and put forth recommendations. The committee recommended that children "should generally be tested only for genetic disorders for which there exists an effective curative or preventative treatment that must be instituted early in life to achieve maximum benefit." They went on to state "that childhood testing was not appropriate for carrier status, untreatable childhood diseases and late-onset diseases that cannot be prevented or forestalled by early treatment." They supported the need for research to determine the appropriate ages for testing and screening for genetic disorders, "both to maximize the benefits of therapeutic interventions and to avoid the possibility of generating genetic information about a child when there is no likely benefit and there is possibility of harm to the child." These recommendations are reflected in guidelines published in later years by other entities (Table 5)

Table 5. Guidelines and Position Statements on Pediatric Genetic Testing

Organization	Year	Recommendations
HDSA Genetic testing for Huntington's Disease	1989	• Testing of children (under 18) is strongly discouraged • If children are exhibiting symptoms of HD, consult a neurologist familiar with HD. Genetic testing may then be recommended as a confirmatory measure in some cases • Minors should wait to have genetic testing until they can arrive at this decision for themselves • Testing of children may expose them to discrimination by health insurance companies, employers, and perhaps their parents
ACMG/ASHG Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents	1995	• Consider potential benefits and harms when deciding whether to test *Benefits – consider genetic testing of children* • Timely medical benefit • Substantial psychosocial benefits (for adolescents) *Deferred benefits – defer testing* • Testing for carrier status • Testing for adult-onset disease *Uncertain benefits – respect family's wishes* • Balance of benefits and harms is uncertain *Harms – defer testing* • Potential harms of genetic testing outweigh potential benefits
AMA Genetic testing of children	1995	*Potential medical benefit (preventive/therapeutic measures available)* • Genetic testing should be offered • In some cases, genetic testing should be required *Conditions with pediatric onset (preventive/therapeutic measure not available)* • Defer to parents' discretion re: genetic testing *Lack of medical benefit (HD)* • Genetic testing of children generally should not be undertaken • Inform families of the availability of genetic tests • Provide opportunities to discuss why tests are generally not offered for children *Carrier status* Defer testing until: • The child reaches maturity • The child needs to make reproductive decisions • Reproductive decisions need to be made for the child *Testing for the benefit of other family members* • Should not be performed unless necessary to prevent substantial harm
NSGC Prenatal and childhood testing for adult-onset disorders	1995	*Testing for adult-onset genetic disorders* • Testing in pregnancy or during childhood should be undertaken cautiously • When testing occurs, it should always include genetic education and counseling

(*Continued*)

Table 5. *(Continued)*

Organization	Year	Recommendations
		• Prenatal testing should be offered regardless of potential for termination • When testing a child or fetus of an individual who declined genetic testing, inform at-risk individual that a positive result may also disclose their status • Exercise caution in communicating/documenting test results • Consider patient autonomy and the principle of nonmaleficence • Need for pilot studies to assess the medical and psychosocial risks and benefits of testing for adult-onset genetic conditions when no direct medical benefit is known • Use extreme caution regarding these tests
AAP Ethical issues with genetic testing in pediatrics	2001	*Newborn screening* • Introduce new tests in such a way to facilitate evaluation of risks and benefits of screening (including efficacy) • Informed consent processes (state level) should foster parental education and promote informed responses to test results *Carrier screening* • Broad use not recommended in children or adolescents • Consider for pregnant adolescents or adolescent planning to get pregnant; fully inform adolescents of benefits/risks of carrier testing *Predictive testing for late-onset disorders* • Defer until adulthood • Defer until mature decision-making possible *In general* • In the absence of immediate medical benefit to the child, decline requests for genetic testing until the child has the capacity to make the choice
ASCO Genetic testing for cancer susceptibility	2003	*Potential medical benefit (i.e., risk reduction available, cancers develop in childhood)* • Defer to parental authority • Encourage testing on clinical grounds *Lack of medical benefit (i.e., HBOC)* • Delay testing until individual informed decisions possible *In general* Advocate for the best interests of the child
ACMG Newborn screening	2006	Recommended actions for an optimal newborn screening system: • National evaluation of conditions and screening technologies • Standardization of case definitions and reporting procedures • Enhanced oversight of hospital-based screening activities • Long-term data collection and surveillance • Consideration of the financial needs of programs to allow them to deliver the appropriate services to the screened population

National Institutes of Health – Department of Energy (NIH-DOE) Task Force on Genetic Testing

In 1997, the NIH-DOE Task Force on Genetic Testing was created and charged with reviewing genetic testing practices in the USA and making recommendations to ensure the development of safe and effective genetic tests. The Task Force concluded (Task Force on Genetic Testing, 1997) that genetic testing was developing successfully in the USA, but highlighted some concerns, which were grouped into four major categories:

(1) the manner in which tests are introduced into clinical practice;
(2) the adequacy and appropriate regulation of laboratory quality assurance;
(3) the degree of understanding of genetics on the part of health-care providers, patients, and the public; and
(4) the continued availability and quality of testing for rare diseases.

The Task Force supported the recommendations on genetic testing of children put forth by the American Society of Human Genetics and the American College of Medical Genetics (The American Society of Human Genetics, 1995). The Task Force's recommendations specifically stated that "Genetic testing of children for adult onset diseases should not be undertaken unless direct medical benefit will accrue to the child and this benefit would be lost by waiting until the child has reached adulthood." The Task Force specifically noted the lack of psychological and social research in pediatric genetic testing. This strengthened their cautious approach: "It is unfortunate that almost no research evidence currently exists on the risks and benefits of genetic testing to teenagers and younger children. We believe that such psychosocial research must be pursued as vigorously as research on issues of analytic validity or utility of tests. However, unless and until such time as contradictory research findings emerge, testing of minors for presumed psychological benefits should be avoided."

Secretary's Advisory Committee on Genetic Testing (SACGT)

In 1998, the Secretary of the US Department of Health and Human Services (DHHS) established the Secretary's Advisory Committee on Genetic Testing (SACGT) http://oba.od.nih.gov/SACGHS/sacgt_info.html. The committee was established in response to the recommendations of the NIH-DOE Task Force on Genetic Testing (see above) and the Joint NIH-DOE Committee to Evaluate the Ethical, Legal, and Social Implications Program of the Human Genome Project. Management of the SACGT was assigned to the Director of the National Institutes of Health. SACGT was established "to help the Nation prepare for some of the revolutionary changes in clinical and public health practice resulting from the continued and increasing use of genetic testing." Specifically, the committee, in consultation with the American public, was asked to assess the adequacy of current programs for assuring the accuracy and effectiveness

of genetic tests and the need for other or additional oversight measures for genetic tests. Following public consultation, the Committee reviewed the public's input and developed recommendations on the adequacy of oversight of genetic testing. Twenty-six recommendations (SACGT, 2000) focused on enhancing the current system of oversight for genetic testing, which is inclusive of issues pertinent to families but not specific to pediatric genetic testing. A key recommendation was that the Food and Drug Administration (FDA) should be involved in the review of all new genetic tests. SACGT's charter was not renewed, paving the way for the Secretary's Advisory Committee on Genetics, Health, and Society.

Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)

In 2002, the Secretary of DHHS chartered the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS; SACGHS, 2002). SACGHS was designed to function as a public forum for deliberation on the broad range of policy issues engendered by the development and use of genetic tests. As warranted, SACGHS was also to provide advice on these issues. Its mandate included consideration of the

- integration of genetic and genomic technologies into health care and public health
- clinical, public health, ethical, economic, legal, and societal implications of genetic and genomic technologies and applications
- opportunities and gaps in research and data collection and analysis efforts
- impact of current patent policy and licensing practices on access to genetic and genomic technologies
- uses of genetic information in education, employment, insurance, and law

In March 2007, SACGHS was charged with investigating specific questions related to the adequacy and transparency of the current oversight system for genetic testing. The committee's report, made public in March 2008 (SACGHS, 2008), highlighted gaps in the oversight system and provided recommendations to maximize the benefits of genetic testing while minimizing harms.

The recommendations not only focused on actions to be taken by DHHS but also emphasized the critical role the private and public sectors play in enhancing oversight. Gaps in five main areas were identified: the regulations governing clinical laboratory quality; oversight of the clinical validity of genetic tests; the transparency of genetic testing; the level of current knowledge about the clinical usefulness of genetic tests; and meeting the educational needs of health professionals, the public health community, patients, and consumers, while providing tools to assist these groups with the interpretation and communication of genetic test results.

While these recommendations are useful in identifying steps DHHS can take in enhancing the oversight of genetic testing, they do not specifically address the challenges presented to children and families considering such testing.

EXISTING GUIDELINES AND PRACTICE STATEMENTS

With the exception of newborn screening, federal policy guiding genomic testing of children does not exist. Consequently, soon after sequence-based genetic testing for a handful of inherited diseases became available in the mid-1990s, various professional organizations and disease-advocacy groups issued position statements and practice guidelines. These were intended to assist health-care professionals working with individuals and families who were considering genetic testing. These guidelines were principally focused on inherited conditions with high penetrance (high risk of disease when a disease causing mutation was identified). While some of the guidelines allude to the complexities that future technologies and knowledge would present, none of them address the specific advances and changes now being seen in genomic technology.

Guidelines and position statements are available from several groups, including the American College of Medical Genetics/American Society of Human Genetics (ACMG/ASHG), the American Society of Clinical Oncology (ASCO), the American Academy of Pediatrics (AAP), the American Medical Association (AMA), the National Society of Genetic Counselors (NSGC), and a number of disease-advocacy groups such as the Huntington's Disease Society of America (HDSA). Table 5 contains summaries of these guidelines and recommendations.

Generally, the guidelines and position statements advocate for a cautious approach to the use of genetic testing in pediatric populations. Health-care providers are viewed as key decision makers and gatekeepers of access to pediatric genetic testing. In the case of conditions that will not develop until adulthood, all of the guidelines in Table 5 recommended deferring testing until the child is able to make an independent and educated decision. Some (ACMG/ASHG, ASCO, AMA) highlight the potential benefits of providing genetic testing to minors at risk for (a) childhood-onset conditions or (b) conditions for which preventive strategies are available. In these cases, the guidelines suggest deferring to the family for a decision regarding genetic testing.

Providers are encouraged to weigh the benefits and harms of genetic testing for minors and to make decisions based on the best interests of the child. According to the guidelines, genetic tests for which there is no immediate medical benefit should be deferred. This includes carrier testing before the time when reproductive decisions need to be made, as well as predictive testing without proven medical benefit.

These guidelines were developed and published approximately 10 years ago. No recent guidelines or position statements have been

proposed[2] which challenge previous guidance. A European group recently published an extensive literature review of publications and position statements regarding predictive and presymptomatic diagnostic testing (Borry et al., 2006) and a survey of European geneticists' attitudes about testing minors (Borry et al., 2008). The European Society of Human Genetics issued draft guidelines based on these findings, which focus on several important factors:

- the centrality of the direct benefit to the minor of genetic testing;
- giving increasing weight to the minor's opinion in proportion to their age and maturity;
- requiring strong participation of the parents or guardians;
- consideration of minors' competency to consent to testing provided they were well informed, had received genetic counseling, and were not pressured;
- emphasizing parental responsibility for informing children about their genetic risk in age-appropriate terms; and
- the absolute necessity of genetic counseling for minors (Borry, Evers-Kiebooms, Cornel, Clarke, & Dierickx, 2009).

The survey of European geneticists (Borry et al., 2008) demonstrated that there is agreement regarding the appropriateness of testing young children when doing so provides a clear medical benefit. However, there is broad disagreement about the appropriateness of predictive genetic testing for childhood-onset disorders for which some treatment or prevention measures are available. Some respondents supported the "rule of earliest onset" and would test no earlier than the first possible onset of disease. Others supported greater parental involvement in deciding whether to proceed with genetic testing in these situations. The authors advocated for harmonization of genetic testing practices throughout Europe. While these recent publications and recommendations from outside the USA are valuable tools for considering the impact of increasingly complex genomic findings on pediatric genetic testing, we await updated consideration from US-based groups.

OVERSIGHT AND REGULATION OF GENETIC TESTING

Oversight of Laboratories Conducting Genetic Testing

Federal agencies, including the Department of Health and Human Services and the Food and Drug Administration, are playing a growing role in the regulation and oversight of laboratories genetic testing. The growing attention is likely due to a combination of events. Multiple bodies associated with federal agencies have published statements on genetic and genomic testing, including the IOM, the Secretary's Advisory Committees,

[2]Exclusive of the core set of diseases proposed by the American College of Medical Genetics for US newborn screening programs.

and the NIH-DOE Task Forces. Additionally, the number of clinically available genetic tests is expanding rapidly. As of April 2010, clinical testing was available for 1720 genetic diseases or disorders, with an additional 255 available as part of research trials (GeneTests, 2008). Consumers are becoming more aware of such testing, through increased media coverage of the genetic and genomic contribution to health and disease, as well as DTC marketing of genetic tests. These factors, combined with the minimal oversight of laboratories conducting clinical genetic testing, have prompted federal agencies to become more involved in the oversight and regulation of genetic services and testing.

Most genetic tests are currently sold as services through clinical laboratories, which are regulated under the Clinical Laboratory Improvement Act (http://www.cms.gov/clia/) and administered by the Centers for Medicare and Medicaid (CMS) and the FDA. CLIA requirements include personnel qualifications, quality control standards, and documentation and validation of tests and procedures. For complex clinical tests, such as genetic tests, CLIA requires periodic proficiency testing, during which the laboratory must demonstrate its ability to accurately perform a test and interpret the results. Private sector organizations provide oversight in partnership with CMS and the Centers for Disease Control and Prevention (CDC), serving as agents for the government as accrediting bodies and developing professional and laboratory guidelines and standards. Although CLIA is a federal act, some states also play a role in the oversight of genetic testing. To date, CLIA has not been amended to include a "genetic testing" specialty. Proficiency testing specific to molecular analysis has not been established nor is it currently mandated through CLIA. Laboratories offering clinical genetic testing must determine proficiency on their own and may or may not use proficiency testing programs established by professional organizations.

The FDA regulates most marketed medical products, including those used to perform genetic testing. However, FDA regulations currently apply only to those products marketed as genetic "test kits," not "home brews." Home brews are developed and assembled by individual labs that use them to collect and analyze samples for genetic testing. These "home brews" are not marketed for use by other labs; rather, they are for the sole use of the lab conducting the genetic test. In contrast, genetic "test kits" are developed by manufacturers and marketed to laboratories, which then use them to perform one or more specific genetic tests. Test kits include everything needed to perform the test, including reagents, instructions, and information on the specific mutations detected by using the kit. Before a test kit can be marketed, the manufacturer must submit data to the FDA, which demonstrate that the test accurately and reliably identified the mutation of interest. The manufacturer must also show that the identified mutation correlates with the present or future health status of the persons who subject themselves to the test.

Of concern is the limited oversight that the federal government exercises over the accuracy (analytical validity) of genetic tests, combined with essentially no oversight of the relevance of the information obtained to health risk (clinical validity). Furthermore, the oversight that does exist

is distributed among several agencies leaving no clear regulatory mechanism to guide the development of genetic tests and their implementation in clinical practice or to ensure analytic or clinical validity of the tests. These concerns are among those targeted by the SACGHS as needing attention.

Oversight and Support for Programs Conducting Pediatric Genetic Testing

A combination of state and federal oversight covers different aspects of genetic testing of children, including newborn screening, the quality of genetic tests, and genetic discrimination. To date, oversight of pediatric genetic testing has focused almost exclusively on improving newborn screening programs throughout the USA. Given the large volume of NBS conducted, NBS deserves special consideration. However, despite its unique ethical complexities, pediatric genetic testing conducted for other purposes, although acknowledged, has not received commensurate attention from policy makers.

Newborn screening within the USA and its territories is undertaken through a state-based public health program that mandates screening of all newborns for diseases that would otherwise not be detected prior to the onset of developmental disabilities, medical problems, or death. Appropriate compliance with recommended medical management allows most affected newborns to develop normally, averting the most significant problems associated with disease. Newborn screening began more than 40 years ago and has operated with limited federal guidance and funding. The Health Resources and Services Administration[3] (HRSA) has played a consistent role, providing resources initially through the Council on Regional Networks for Genetic Services (CORN), and more recently through the National Coordinating Center for the Genetics and Newborn Screening Regional Collaborative Groups (NCCRCG) and the National Newborn Screening and Genetics Resource Center (NNSGRC) (National Newborn Screening & Genetics Resource Center, 2008). The NCCRCG includes seven regional collaborative groups (RCs) and has as its goal improving the health of children and their families by promoting the translation of genetic medicine into public health and health-care services (http://www.nccrcg.org/). The RCs use a regional approach to address the issues of distribution of genetic services and resources, with the goal of strengthening and supporting the genetics and newborn screening capacity of the states and the nation. The NCC and RCs have a cooperative agreement with the American College of Medical Genetics. The NNSGRC provides information and resources on newborn screening and genetics to benefit health-care professionals, the public health community, consumers, and government officials (http://genes-r-us.uthsca.edu). The NNSGRC web site gathers information on newborn screening, including committee reports and fact sheets, and provides a message

[3]The Genetic Services Branch of HRSA's Maternal and Child Health Bureau serves as the federal focal point for the development, monitoring, implementation, and evaluation of national programs for genetic services and newborn screening.

board forum for consumers of newborn screening services. In addition to the regional centers, this effort provides for a National Coordinating Center designed to enhance and improve the ability of state and local public health agencies to provide screening, counseling, and health-care services to newborns and children at risk for or having heritable disorders. HRSA has also published "action sheets" for several disease categories as clinical resources, which have been adopted by the American College of Medical Genetics and state newborn screening programs. Other federal guidance includes the National Committee for Clinical Laboratory Standards' (NCCLS) "Standard on Blood Collection on Filter Paper" which provides minimal guidance to state-based programs. Finally, the National Advisory Committee on Heritable Disorders in Newborns and Children, chartered by the Department of Health and Human Services (DHHS), provides formal recommendations to the Secretary of Health and Human Services about the department's role in advancing newborn screening programs.[4,5]

The resources available at the state level to support NBS and necessary clinical follow-up vary. Early diagnosis may save states money, but linking children into coordinated systems of follow-up and care incurs additional costs (National Conference of State Legislatures, 2008). Funding decisions are at the state level, including state budget appropriations and fee assessments (National Newborn Screening & Genetics Resource Center, 2008).

The disorders included on state NBS lists differ from state to state, as do the resources provided to physicians and families caring for these children. To address this issue, the MCHB commissioned the ACMG to outline a process for the standardization of guidelines and outcomes for state NBS programs. This included the development of a uniform panel of conditions to be included in all state NBS programs.

In 2006, the ACMG published 29 conditions for which newborn screening should be mandated (The American College of Medical Genetics, 2006). An additional 25 conditions were offered for consideration. These additional 25 conditions (1) were part of the differential diagnosis of the panel of 29 core diseases, (2) are clinically significant conditions revealed with screening technology, but lack efficacious treatment, or (3) represent incidental findings for which there is potential clinical significance. The proposed list of diseases is anticipated to identify an additional 1,000 babies each year with treatable metabolic and endocrine disorders.

The Advisory Group on Heritable Disorders strongly endorsed these guidelines and urged the Secretary of Health and Human Services to facilitate broad implementation across the nation, but the ACMG report is not without its critics who consider the recommendations to be overbroad. Bioethicists have urged caution in expanding newborn screening panels,

[4]This committee has strongly recommended that the Secretary initiate facilitate adoption of the ACMG recommended screening panel by every state newborn screening program.

[5]http://www.hrsa.gov/heritabledisorderscommittee/reports/letterstoSecretaryofHHS.htm

pointing to false-positive test results, and concerns about population-wide screening of asymptomatic individuals (Botkin et al., 2006). Others, including members of the US Preventive Services Task Force, have expressed concern about its report stating the ACMG was too hasty in embracing newborn screening for poorly understood, untreatable diseases in part based on a "technological imperative," i.e., including these diseases in large part because now the technology exists to easily test for them, and multiplex platform testing makes it easy to add additional targets (Moyer, Calonge, Teutsch, & Botkin, 2008). The President's Council on Bioethics strongly disagreed with the ACMG guidelines, stating that "the potential benefits of mandatory, population-wide newborn screening for diseases for which there is no current treatment are outweighed by the potential harms" (Bioethics, 2008). The Council recommended that the states mandate newborn screening only for diseases that meet traditional criteria: (1) the disease must pose a serious threat to the health of the child; (2) its natural history must be well understood; and (3) timely and effective treatment must be available, so that the intervention as a whole is likely to provide a substantial benefit to the affected child. The Council encouraged states to conduct pilot studies with appropriate informed consent to explore testing for other conditions. In light of the fact that many states have moved toward adopting the ACMG recommendations, this cautionary warning may go unheard.

Policy issues arise because of the lack of federal oversight and regulation, as well as the need for state legislatures to budget for these programs. Federal panels, such as that convened by the MCHB, may recommend the inclusion of certain disorders on the NBS panel, but lack of federal funds to assist states with funding these initiatives is a serious oversight. A lack of consistency across states means that children may be screened for a condition in one state but not in others. This can affect diagnosis of the disorder, access to health care, and eventually, cost of providing care to that individual (ACMG, 2006).

While newborn screening remains largely a state-controlled effort, a federal law was passed in April 2008 to provide for more consistent newborn screening practices across the nation. The Newborn Screening Saves Lives Act, sponsored by Senator Chris Dodd (D-CT), provides grant money to states for education and outreach on newborn screening; incentivizes states to adopt and implement screening for the full panel of disorders recommended by the Advisory Committee on Heritable Disorders in Newborns and Children; reauthorizes and expands the role of the Advisory Committee to continuously revise and update the panel for recommended tests; and establishes a clearinghouse within HRSA to be available on the Internet to provide current educational and family support information, resources, and data on newborn screening.

Legislative Efforts and Regulatory Actions

The US Congress has been interested in and concerned about genetic testing for some time, with multiple legislative efforts to address various aspects of genetic testing and protection of genetic information. Since

the inception of the Human Genome Project, a primary concern among scientists has been the lack of federal protection against genetic discrimination. Research has demonstrated that fear of losing health insurance is a top concern of individuals from at-risk families who are contemplating genetic testing for a familial disorder (Hadley et al., 2003). Finally, after a 13-year legislative effort, this issue has been addressed, and in May 2008, the Genetic Information Non-Discrimination Act of 2008 became law. Commonly referred to as "GINA," this federal law prohibits the use of genetic information, including family history, for any health insurance or employment decisions and provides important civil protections against discriminatory uses of an individual's genetic information.

Regarding the issues of test quality, two bills that address this area were introduced in March 2007: the Laboratory Test Improvement Act (S. 736), introduced by Senator Edward Kennedy, and the Genomics and Personalized Medicine Act of 2007 (S.976), introduced by Senators Barack Obama and Richard Burr. The Kennedy bill would require all laboratories performing genetic tests not presently regulated by the FDA to submit data on clinical and analytical validity to the FDA for review and posting to a public-access registry. The proposed legislation would also require the CLIA program (managed by the Centers for Medicare and Medicaid Services) to establish a new specialty area for genetic tests that would require proficiency testing of all labs performing genetic tests, a quality control currently absent from CLIA regulations. The Obama/Burr bill would establish an interagency working group to coordinate and standardize all federal efforts related to genomics initiatives, improve genomics workforce training, and require analysis of DTC marketing practices. Like the Kennedy bill, this bill would also require the CLIA program to establish a specialty area for genetic tests.

In response to the absence of federal regulation in this area, some states have taken strong regulatory positions to limit DTC of genetic tests. For example, in June 2008, the state of California issued "cease and desist" letters to 13 genetic testing companies for violating state law that requires clinical lab tests offered directly to consumers to be ordered by a physician (Ravn, 2008). The state of New York has also sent warning letters to more than 30 DTC companies advising them of licensing requirements to solicit DNA samples from New York residents (Baker, 2008). In light of these recent legislative and state enforcement efforts and the growing interest in personalized medicine, it is very likely that Congress will address regulation of genetic testing in some comprehensive fashion in the coming years.

CHALLENGES

Predictive and presymptomatic genetic testing for adult-onset conditions has been available for more than 10 years, yet the policies available to help guide the application of these technologies in genetic testing of children lag behind. In the effort to regulate and guide the use of genetic and genomic tests in children, many diverse challenges lie ahead.

Efforts to regulate laboratories conducting genetic testing are moving forward through committees appointed by the DHHS (SACGT, SACGHS), the work of the FDA and advocacy groups such as the Genetic Alliance. However, significant work remains in order to ensure that the recommendations for regulating laboratories conducting genetic testing, as proposed by SACGHS in 2008, are implemented. Additional challenges include developing and implementing professional and public education programs on genomics. Such programs are necessary to facilitate professionals' knowledge of genomic technologies, improve their readiness to educate and counsel their patients, and educate professionals and the public about the potential uses, risks, benefits, and limitations of evolving genomic technologies.

As outlined within this chapter, numerous professional bodies have issued guidelines and statements that generally address the issues associated with genetic testing in children and provide useful guidance as to when or under what circumstances genetic testing is appropriate to consider during childhood. Although not without limitations, these guidelines assist health-care providers and families in sorting through the relevant issues. As recommended, genetic testing in children has generally been limited to diseases and disorders that have medically preventable or treatable consequences during childhood. Furthermore, most genetic testing to this point has been provided under the oversight of genetics specialists, who promote a comprehensive and conservative approach to considering genetic testing. Under these circumstances, the existing guidelines may have provided sufficient direction.

However, as genomic technologies advance and genetic and genomic testing become more common, expanded federal oversight of the clinical applications of genomic testing in children and their adult relatives may be in order due to a number of issues likely to arise. First, the number of genomic tests will continue to increase and will include characteristics, traits, or diseases without medically available treatments or prevention strategies. Second, genomic tests will increasingly be offered through primary health-care providers, who may not be sufficiently trained in genetics and genomic sciences to provide adequate guidance to children and families considering testing. Finally, the availability of direct-to-consumer genetic and genomic tests will likely increase, providing opportunities for genetic or genomic testing that takes place outside or with limited involvement of the health-care system. While current or future legislative efforts could slow or suspend commercial opportunities for DTC tests, genomic testing is likely to become increasingly available through other routes.

The decision about whether federal oversight of genetic testing in children and families is necessary also comes with significant obstacles. Ideally, such policy would benefit from research that informs its development. As elucidated within this chapter, very little research has been conducted in this arena; that which exists includes small samples of children and parents and has focused on single-gene disorders. Furthermore, the diseases studied differ on such characteristics as age of onset, the availability of options for treatment or prevention, and the risks of the associated condition (e.g., medical versus developmental, serious versus

minor). This variability may limit the general application of the findings and may not provide an adequate basis for consideration of the potentially diverse set of psychological, medical, and social issues facing children in families with vastly different kinds of genomic conditions. Developing policy pertaining to genomic testing in children is further complicated by the continually changing technology used in genomic testing and the rapidly increasing numbers of available tests. Therefore, the development of overarching policy pertaining to the clinical application of pediatric testing for genetic and genomic diseases remains challenging and will necessarily need to remain "fluid" for the foreseeable future.

Current federal oversight of genetic testing is problematic in that it is distributed among several agencies. This leaves no clear regulatory mechanism to guide the development of tests from research to clinical practice or to ensure that the tests are analytically or clinically valid. As recommended by SACGHS, the identification of a lead agency responsible for oversight and regulation could benefit the process. Which agency should take the lead is a matter of some debate, although possibilities include the FDA, the NIH or the CMS.

Direct-to-consumer (DTC) genetic testing presents new and different challenges in the clinical application of genomic sciences. In DTC testing, genomic and genetic testing are offered directly to the general public, often via the Internet or through print advertisements. This typically occurs in the absence of health or medical professionals, who could assist in the interpretation of the information provided or its application to medical well-being. Some companies provide information to consumers about genetic variants associated with serious health outcomes that may require intervention, such as diabetes, heart disease, and Alzheimer's disease. The lack of involvement of knowledgeable professionals to educate and counsel patients and help them interpret genetic test results is concerning. The presence of genetic variants associated with disease may not equate to direct health risk. In certain cases, genomic testing may detect changes in DNA sequences that are associated with disease; but these mutations may never manifest into disease for unclear reasons (Wheeler et al., 2008). Receiving this type of medical information without an accurate framework for understanding it can create the "worried well," healthy people who are now concerned that they will develop a disease based on their genetic makeup. Receiving such information could also create "worried would-be parents," who may decide against having children based on genetic tests for which insufficient evidence is available to truly inform medical or reproductive decisions.

Concern is also raised about privacy and confidentiality of genetic information following DTC genetic testing. While most commercial companies state that they destroy biological specimens (e.g., saliva, cells from a cheek swab) after testing, many retain the actual data for undisclosed research purposes. Thus, consumers' genetic data effectively become the property of the testing company, and they typically do not consent to its future uses or releases. Even if data are stripped of traditional identifiers (e.g., name, social security number, date of birth), a large enough volume of genomic data can result in reidentification through other means,

particularly when the genotypic and phenotypic data are made available (Lowrance & Collins, 2007). There has already been at least one occurrence of identification of an individual through online genetic testing services (Stein, 2005).

Internet-based DTC genetic testing also presents questions of sample ownership. It would be difficult to obtain adequate saliva samples from someone without their knowledge; however, an individual could submit a DNA sample from another person and claim it as their own, thus gaining access to personal genetic information. A parent could take a cheek swab sample from a child and send it for analysis without the child's consent. Because the data from these DTC analyses may live on in de-identified aggregate data sets that provide enough information for individual identification, the parental decision to utilize this type of testing on children could have privacy ramifications that cannot now be imagined.

The concept of personalized medicine is receiving a growing amount of attention. Providing an individual with a personalized approach to health care is based on knowing the genomic makeup of that individual and prescribing life style considerations, preventive strategies, and treatment based on that individual's personal genome. Technology that allows complete analysis of one's entire genome is rapidly improving and decreasing in cost. This may soon result in the ability to assess thousands of genes, affording the potential to identify mutations and sequence variants increasing (or decreasing) risks for a multitude of diseases within a single individual. The application of whole genome technology adds significant complexity to the issues under discussion as consideration of genetic testing to date has focused on risk for a single disease rather than multiple diseases. Such testing will provide a "report card" of sorts, detailing disease risks based on genomic information. Some disease risks may have preventive options available while other risks may not. Who will decide when such testing will (or will not) be done and when it will be undertaken? Will the provision of multiple disease risks affect self-concept, desirability, level of stigma, and family or social relationships? In the absence of research that explores the impact and utility of genomic testing, concerns exist regarding its implementation and impact, most notably if such testing is initiated during childhood.

CONCLUSIONS

While the regulation and oversight of laboratories conducting genetic and genomic testing is moving forward and addressing issues of quality control and efficacy, the regulation and oversight of the clinical provision of such services is lagging behind particularly when considering genomic testing in children. In developing policy on genomic testing of children, input will be necessary from a host of stakeholders. These include parents of children for whom genetic testing is currently possible, health-care professionals who will be involved in providing information about and facilitating genomic testing, laboratories conducting genomic testing, the general public, and policy makers. As reported, a limited pool of research

exists on parents and children's views of carrier and susceptibility testing during childhood. However, findings presenting parents' views generally conflict with the current guidelines. Parents often prefer that testing be conducted at early ages even in the absence of evidence of tangible medical, social, or psychological benefits, while current guidelines generally recommend delaying testing until adulthood. It is critical that the various stakeholders engage in thoughtful dialogue to move toward a more cohesive view.

The development of policies pertaining to genomic testing in children is far more complicated than the development of policies pertaining to genetic testing. The range of information available from genomic testing will be considerably broader and will include a multitude of genomic-based risks, ranging from smaller risks for common diseases to high risk for adult disease and identification of carrier status for recessive diseases. Wilfond & Ross (2009) suggests that the tension between assessments of benefits and risks made by policy makers and health-care providers and the authority owed to parents in making health-care decisions on behalf of their children will be tested as the ability to conduct and interpret whole genome analyses continues to move forward. He encourages that determination of what limitations, if any, to be imposed on genomic testing during childhood should be in place before the commercial availability of such testing. This approach is in contrast to a US health-care system, which has often been described as reactive rather than proactive.

Developing policy(s) related to genetic testing of children and their families will necessarily need to be "fluid" as the explosion of technology unfolds and eventually translates into effective prevention strategies and treatment approaches. As the evidence suggests, one size will not fit all when it comes to guidelines or policy for genomic testing of children.

APPENDIX

Case Scenario 1

Pediatric Genetic Testing for Diagnostic and Medical Management Purposes

A comprehensive examination of the child depicted in Figure 1 (Individual III-5) included a genetics physical examination, collection and review of family medical history, a neurological examination, electromyography (to evaluate and record muscle signals), and nerve conduction velocity studies (to evaluate the function, especially the electrical conduction, of the motor and sensory nerves). This led to a preliminary diagnosis of spinal muscular atrophy (SMA). SMA is an autosomal recessive condition, which results in progressive muscle weakness due to the loss of lower motor neurons in the spinal cord and brain stem. Individuals affected with SMA have mutations in both copies of either the *SMN1* or the *SMN2* gene. After comprehensive education and counseling, the child's parents elected to pursue genetic testing, with the hope of finding a specific cause for their

child's progressive muscle weakness. Testing of the child's blood sample demonstrated the classic SMA mutation in both copies of SMN1, suggesting that both parents are unaffected carriers of a mutation in one copy of SMN1. Based on this information, the parents have a 25% chance of having another child affected with SMA each time a pregnancy is conceived. Given the incidence of non-paternity within the USA, if private conversations with the mother indicate that non-paternity should be considered, carrier status should be confirmed through molecular testing. Approximately 1 of every 50 people in the USA is an unaffected carrier of an SMA mutation, making it relatively common. The identification of such mutations within the immediate family (parents and child) simultaneously identifies risks for more distant family members, i.e., siblings of the child, uncles/aunts, and grandparents.

SMA has different levels of severity. Given the age at which this child developed symptoms, she would be classified as having SMA II and would be expected to have normal cognitive development; however, her gross motor development will be hampered, and she may only be able to sit independently. Unfortunately, this skill is often lost by the mid-teens, and wheelchair dependence is inevitable. The literature suggests that about 70% of persons with SMA II are still alive by the age of 25 years. Based on the diagnosis, questions about the future will need to be addressed, including appropriate medical, educational, socio-legal preparations; however, this is often very challenging to address with the family.

Case Scenario 2

Carrier Testing

Reconsidering the pedigree presented in Figure 1, carrier testing might be of interest to several family members to determine if they carry a single copy of the mutation for SMA. This would provide information about their reproductive risks (e.g., risks to future offspring). For example, the partner of the index case's maternal uncle (II-5) is currently pregnant (12th gestational week). They have close contact with the affected child and observed her developmental difficulties. Having lost a previous pregnancy, they have expressed interest in knowing if the father (II-5) carries the SMA mutation, increasing the chances that the child of the current pregnancy could be affected. With ample time remaining for testing during this pregnancy, carrier testing would first be conducted on the father; if he is a carrier, then carrier testing would be conducted on his partner. If both prospective parents carry a SMA mutation, prenatal genetic testing for SMA could be considered for the current pregnancy. Although professional guidelines suggest that carrier testing is most appropriate when considered by an adult following education and counseling, and conducted outside of pregnancy or other stressful life events, this is not always possible, as this scenario presents.

Other family members might also express interest in carrier testing for themselves or their children to clarify reproductive risks. As seen in

Figure 1, the mother of the affected child has a 12-year-old son (III-6) with a previous partner and would like her son to have carrier testing. Limited research exists to guide such requests, with conflicting results and conclusions. Some parents maintain that they are in the best position to make decisions about obtaining information about their child's genetic status for the disease in their family and educating their child about their status. However, parents deciding to have their child undergo carrier testing precludes the right of that child not to know their carrier status. Certainly, parents may involve a child in the education and counseling leading to a decision regarding carrier testing. However, in the absence of emotional maturity, a child's assent leaves the parent in a position of power.

After several months of periodic contact between the family, the Pediatrician, and the Genetics team, the index case's half-brother (III-6) was able to express to his parents his lack of interest in knowing his SMA carrier status at this point in time. He verbalized that he would most likely want to know at a time when he is considering having children. He was also able to express concern about knowing his carrier status. Despite his mother's initial strong interest in knowing his carrier status, his verbalization of concerns and thoughts about carrier testing curtailed her initial urgency to pursue testing.

Case Scenario 3

Presymptomatic Testing for Disease Potentially Presenting During Childhood

The family depicted in the pedigree presented below (Figure 2) has an autosomal dominant inherited cancer susceptibility syndrome known as multiple endocrine neoplasia, type 2 (MEN 2). MEN 2 poses certain risk for thyroid cancer, along with other health risks. Three MEN 2 subtypes have been identified; MEN 2B causes medullary thyroid cancer (MTC) in early childhood. Thyroid cancer associated with MEN 2 can be prevented by prophylactic thyroidectomy (removal of the thyroid prior to the onset of disease), the timing of which depends on the specific mutation identified within the RET gene. For the family described in Figure 2, surgery is recommended before age 5.

Carriers of mutations in the RET gene often demonstrate other physical features suggestive of MEN 2 (e.g., distinctive facial features, tall lanky body, and characteristic findings of the lips and tongue). However, molecular genetic testing provides early identification of at-risk family members, improving diagnostic certainty and reducing the need for costly screening procedures in family members who have not inherited the disease-causing mutation. While prophylactic removal of the thyroid eliminates the risk of thyroid cancer, other health screening is necessary due to increased risk for pheochromocytoma. A pheochromocytoma is a rare tumor that develops in the core of adrenal glands, which sit above each kidney and produce essential hormones. Pheochromocytoma can cause the adrenal glands to produce too much of certain hormones, raising blood pressure and heart rate to potentially life-threatening levels if not treated. Screening

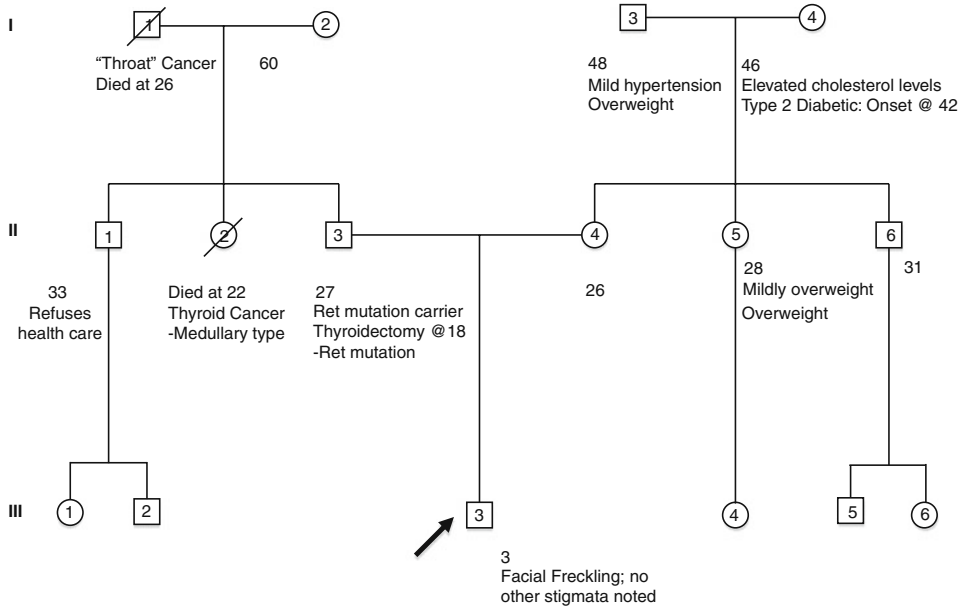

Figure 2. Pedigree of family with MEN 2B.

for pheochromocytomas include annual biochemical screening, followed by MRI if the biochemical results are abnormal.

In the family illustrated in Figure 2, the 3-year-old boy (III-3) has a 50% risk of inheriting the RET mutation known to be carried by his father (II-3). After careful discussions with both parents, genetic testing for the known RET mutation will be completed to clarify the boy's mutation status. Should he carry the familial mutation, surgery would be recommended prior to his fifth birthday. While his father demonstrates the classic physical features of MEN 2B, the 3-year-old boy demonstrates facial features reminiscent of both parents. His mother openly shares her belief that her son will not have the mutation carried by his father. While she may be correct in her assessment, the Genetics professionals are careful to recognize her response as an attempt to deny the empiric risks faced by her son. Genetic testing a full year ahead of when surgery might be needed provides adequate time to help the parents anticipate and prepare for the possible outcomes of testing, which, ideally, will assist their adjustment to outcome.

Case Scenario 4

Presymptomatic Genetic Testing for Adult-Onset Disease During Childhood

The family depicted in the pedigree below (Figure 3) has an inherited cancer susceptibility syndrome known as Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC). A person who carries a single copy of a mutation in one of four genes associated with this syndrome

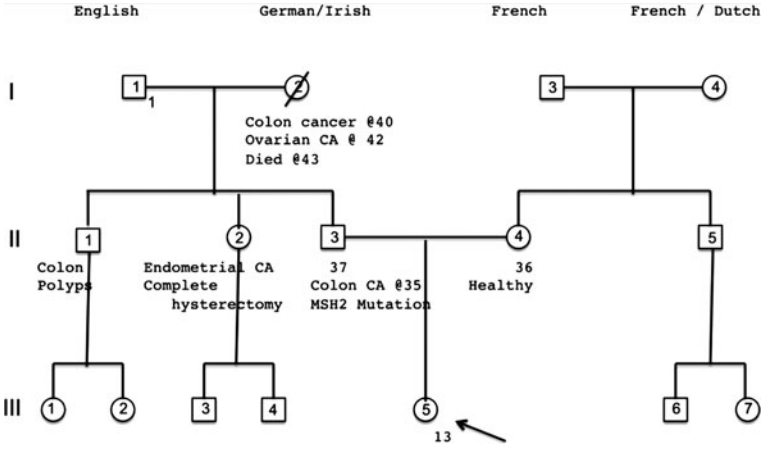

Figure 3. Pedigree of family with Lynch syndrome.

has significant risks for multiple cancers, most notably cancer of the colon, endometrium (uterine wall), stomach, and/or ovaries. Colonoscopy can significantly reduce the chances of colon cancer, by removing polyps before they become cancerous, or decrease the severity if cancer does occur, by identifying cancer early, which results in an improved prognosis. Women have significant risks for endometrial and ovarian cancer, for which cancer screening is less effective. Some women may consider having a complete hysterectomy (removal of their uterus and ovaries) after completion of childbearing as one way to reduce their cancer risk. The cancers associated with Lynch syndrome occur during adulthood. Genetic testing for adult-onset disease is typically postponed until after 18 years of age, with hopes that this will facilitate "mature" consideration of the risks and benefits of genetic testing, allow an informed decision about testing, and facilitate coping and adjustment to results.

The father (II-3) depicted in Figure 3 is known to carry his family's mutation for Lynch syndrome and was diagnosed with colon cancer at 35 years of age. His mother (I-2) was diagnosed with colon cancer at 40 and ovarian cancer at 42, which was at an advanced stage and ultimately took her life. The father was 17 at the time of her death and recalls her experiencing tremendous suffering and pain as a result of the ovarian cancer. Her death presented a lasting hardship upon their family, as few relatives were around to help fill the void of his mother's absence. Understandably, he has palpable fear of recurring cancer for himself and overwhelming concern for cancer affecting his children. He states that his greatest fear is for his daughters. He is adamant that his 13-year-old the daughter (III-5) should undergo genetic testing now so that they can begin to plan her life should she be found to carry the family mutation. He suggests that she could have children at an early age, so that she could undergo a complete hysterectomy and reduce the chances that she experience what his mother went through. In speaking with her pediatrician, the daughter acknowledges her father's worries about cancer; however, she is not ready

to face such big decisions and really just wants to focus on school, soccer, and her friends. She has never told her father how she feels, as she knows how important this is to him.

Case Scenario 5

Genetic Testing for Obesity: A Challenge for the Future

The mother (Individual II-2) in the pedigree in Figure 4 brought her oldest child (individual III-5), age 9, to her primary health-care provider (PCP) for a well-child checkup. While completing the height and weight measurements, the nurse notes that the child is at the 80th percentile for weight and the 50th percentile for height for her age. At her last visit, 2 years earlier, she had been at the 50th percentile for weight and height. The nurse tells the PCP of the new measurements and expresses concern about child III-5's rapid weight gain.

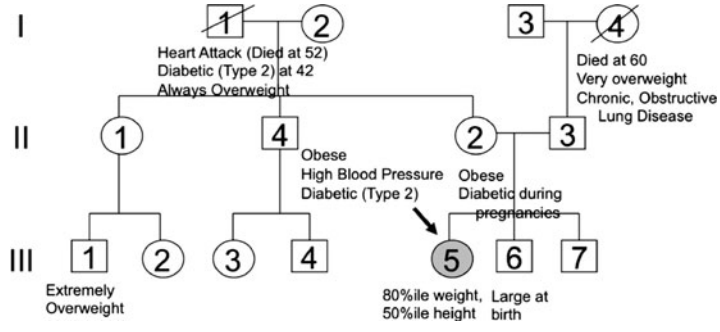

Figure 4. Pedigree of family experiencing obesity.

During the visit, the PCP asks the child's mother if she has noticed any changes in her child's appearance or eating behaviors. The mother indicates that her daughter has started eating foods high in sugar and salt in between meals, and the mother often feels like her daughter is "eating her out of house and home." She is particularly concerned because she (the mother) is overweight, as is her husband. The family history reveals that several biological relatives have died of obesity-related causes (see pedigree below). Further questioning reveals that the girl thinks she is bigger than any of the other kids in her class, and that she is teased and mocked at school for her size. While not yet technically obese, the daughter's weight is high for her height, and she has the potential to become obese during adolescence or early adulthood.

The PCP talks with the child and her mother about healthy food choices and portion control. She refers the family to a registered dietitian for more help making healthy choices at meal and snack times. At the end of the visit, she mentions to the mother that genetic testing for obesity has recently become available. Acknowledging that little is known about the genetic basis of obesity, the PCP asks whether they would be interested in pursuing genetic testing for the most common genetic markers associated with obesity.

Obesity is a complex condition, in which biological (biochemical and genetic) and behavioral (diet, exercise habits, etc.) factors interact to result in the expression of the phenotype of interest (e.g., obesity). Genetic testing is currently available for rare, monogenetic (single-gene) disorders but is not yet available to identify more common genetic factors associated with obesity in the general population. Recent advances in genomic sciences (genome-wide association studies) suggest that genetic testing for complex diseases and characteristics may not be far off. However, interventions specific to the identified genotypic differences (e.g., pharmacogenetic approaches) may never be available or make take many years to develop. This leaves persons considering genomic testing for obesity with the same alternatives for weight loss as others in the general population (diet modification, exercise programs, etc.) leaving the benefit of such testing unclear.

Genetic testing of children for a condition such as obesity is necessarily more complicated than diagnostic or medical testing. Recent studies estimate that obesity in children is likely to have a genetic contribution of about 77% (Wardle et al., 2008); however, this means that the remaining 23% of variation likely has a behavioral component. While genetic testing for obesity might provide valuable information on whether an at-risk child is likely to become obese, there are other issues to consider. One major question is whether providing genetic risk information for a condition such as obesity will lead to behavior changes, resulting in a different phenotype than if those behavioral changes were not implemented. Obesity is also a stigmatized condition; revealing that a genetic predisposition is partly responsible for an obese person's weight might result in a lower level of stigma. Additional questions include the penetrance of any obesity-related genetic variations (e.g., how likely is it that the child who tests positive for an obesity-related variant will go on to become obese); the possibility that parents of a child with a tendency toward obesity will change their behavior toward that child; and the possibility that stigma and discrimination will not be eliminated even when obesity is found to have a genetic, unchangeable, component.

After consultation with a genetic counselor regarding genetic testing of child III-5 for obesity-related genetic variants, her parents chose not to have her undergo genetic testing. Instead, the family is making changes in food choices and increasing their overall level of physical activity in order to limit their daughter's weight gain.

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22

Training, Practice, and Collaboration: New Opportunities for Pediatric Psychology and Genomic Medicine

ANDREA FARKAS PATENAUDE

INTRODUCTION

Medical practice and the research that underlies it are radically changing due to advances in genetics and genomics (Guttmacher & Collins, 2005; Joshi & Kucherlapati, 2008). The impact of genetic medicine has been felt more immediately in adult than in pediatric settings. However, pediatric psychologists working in oncology, psychiatry, or many other medical settings will very soon need to be up to speed on genetic concepts and on the psychosocial implications of genetic advances as they permeate pediatric practice.

Pediatric genetic research aims not only to better understand diseases of childhood but also to study the precursors and gene–environment links which presage the development of disease in adulthood (Cheng, Cohn, & Dover, 2008). "Overwhelming evidence suggests that gene-environment interactions very early in development have profound effects on the emergence of adult diseases such as diabetes, cardiovascular disease, cancer, and psychiatric illness ... Clinicians who care for children will have the first opportunity to 'predict' and 'preemptively' intercede in the progression of these disorders, thus translating genetics to practice, policy, and communities" (Cheng et al., 2008).

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Genetic testing is currently used with children who have diseases known or suspected to be due to a hereditary susceptibility, especially where knowledge of the child's genetic status may influence treatment choices. It is also used for presymptomatic testing of children at risk for rare disorders for which targeted screening regimens during childhood or genetic treatments are available. Genetic testing will likely be used in increasing measure in the near future for genetic screening of children for more common disorders of childhood and adulthood. It will also be increasingly utilized in children for determination of pharmacogenomic risk for medication side effects or likelihood of benefit. In addition, genetic studies may help ascertain risk for late effects in children who have had serious diseases, such as a childhood cancer.

The training of pediatric psychologists will henceforth need to include at least basic understanding of genetic concepts and awareness of the diseases where genetic advances are already or will likely soon play major roles in the treatment of children. Psychologists will need to be aware of the psychological impact of the emotional, financial, ethical, and social implications that designation of a disease as a genetic disorder carries with it. Ethical considerations related to proxy consent and assent and communication to children about genetic testing will also be important. Psychologists will need to consider how to develop fruitful collaborations with genetic counselors, geneticists, nurses, pediatricians, and other pediatric specialists in order to deliver needed services in a comprehensive manner to families for whom genetic illness is a reality. Pediatric psychologists will also work with researchers who plan to involve children in genetic studies and with ethicists in developing policy about the involvement of children in genetic research.

This is an exciting era in medicine. The Human Genome Project has led to the beginning of the era of personalized medicine. The path to personalized medical care, however, is an uneven one, as the genetic underpinnings of some diseases will lead more quickly than others to clinical translation, affecting clinical practice. While those who are the first to reap the benefits of this new information may be considered to be lucky beneficiaries of genetic progress, they are also the pioneers in being the first to experience the social and psychological impact of genetic medicine and to confront the ethical dilemmas which emerge from utilization of this new technology. Guidelines about the use of genetic information are emerging from a number of different professional organizations (National Cancer Institute, 2006; British Society for Human Genetics, 2006). There is not, however, universal consensus, especially in pediatric research contexts, about how or when information should be shared or protected (Patenaude, Senecal, & Avard, 2006). Nor is there consensus in specific cases about when genetic testing can ethically benefit children and when children should be protected from potentially discriminatory or upsetting introduction of genetic knowledge.

This complicates the training of pediatric psychologists who wish to work in areas where genetics plays an important role or where it will soon play such a role. We will review the genetics competencies which are recommended for all clinical professionals, will discuss the guidelines which

pertain particularly to pediatric practice, and will consider the particular dilemmas which genetic information gives rise to. We will refer to what has been learned from the past decade of research into adult hereditary cancer syndromes and highlight how these data can and cannot be translated into practice involving children.

HOW IS GENETIC INFORMATION DIFFERENT?

Pediatric psychologists already learn a great deal about illness in children and its emotional and social ramifications. Henceforth, consideration of how hereditary disease differs from sporadic illness in its individual and familial impact should also be taught. Over the past few decades we have come to accept that illness in an individual family member has emotional ramifications for the other members of the family which must be attended to if comprehensive care of the patient is the goal. With genetic conditions, the framework of comprehensive care is considerably larger, since it is not only the emotional well-being of the patient and immediate family members which is affected by the diagnosis but also the risk for physical disease in other family members, including extended family, which is directly affected by the diagnosis of one individual. Thus the shock waves which permeate a family after diagnosis of serious hereditary disease are likely to be much more intense and far-reaching (Fanos, 1997). When a young child in a family is diagnosed with a sporadic cancer, for example, the family typically coalesces around that child and his/her parents to provide support. When the child's cancer is found to be part of a hereditary condition, especially one responsible for disease in both adults and children, a wide circle of blood relatives in multiple generations are simultaneously identified as being at increased and, sometimes, immediate risk. Thus, there may also be great energy invested in thinking about the implications of the genetic medical information for many other relatives. Decision making about the need for and timing of genetic counseling and testing of siblings, parents, aunts, uncles, and cousins may require additional hospital visits and add to the emotional stress on family members. With the increased complexity of the issues, it is increasingly likely that whatever is difficult in the family's communication dynamics is likely to be aroused, further complicating the family's interactions and emotional burdens (see Table 1).

Other issues arising especially in families with a predisposition for serious, inherited disease affecting children include the increased guilt and worry which such knowledge may engender in parents. Parents feel guilty whenever their children become ill, but the guilt can be intensified when it is clear that the predisposition to serious disease was inherited from one parent. These feelings can also lead to disagreements and bad feelings between parents either for "causing" the disease in the child, for differences in how the condition or communication about the condition should be handled, or because one parent feels the other is not handling well the feelings of guilt (Arribas-Ayllon, Sarangi, & Clarke, 2008). Because genetic predisposition testing can, at least theoretically, be done at birth,

Table 1. Psychological Issues in Pediatric Cancer Genetic Testing

Issue	Concerns	Role of the Pediatric Psychologist
Distress	Child worries will develop cancer; parental worry about ill child and risk of other children	Help parents to differentiate immediate and more distant priorities threats. Correct misinformation or direct to those who can. Encourage appropriate coping and communication
Guilt	Parents' guilt of passing on deleterious gene; child guilt for worrying parents or, if negative, for being spared	Help parents differentiate what they cannot control and what can be done with genetic information to protect their child. Help relieve child of burden of responsibility
Family discord/parental overprotection	Identification of unaffected mutation carrier may encourage parental "hovering" or overprotection	Encourage discussion of medically appropriate screening and age-appropriate separation. Give older children more information and responsibility for self-care
Misinformation/mis-expectation	May belief developing disease is inevitable, that screening increases disease risk or, conversely, that genetic cures are all commonly available now, etc.	Clarification of meaning of test results, risks, and knowledge of screening recommendations. Refer back to or consult with genetics professionals, as needed
Secrecy	Family members may avoid sharing genetic information with some parts of family or with some children	Discussion of family dynamics, values, and developmental and emotional level of children in family can help develop plans for communication which do not burden children
Help in talking to children	Parental uncertainty about appropriate time to inform children, language, and method	Discussion between parents and rehearsal of talking to children can reduce stress in talking to children
Reproductive decision making	Parental concerns about having additional children; concerns of older adolescents and young adults about life planning and risk of passing mutation	Discussion of motivations, fears, family dynamics, timing. May discuss options of preimplantation genetic diagnosis, other technologies. Encourage recognition technology may improve in future years

there may be many decades of anticipatory worry for parents about symptoms which might (or might not) signal the onset of the hereditary disorder in their children. In turn, children who are not ill can experience such parental concern as overprotection, which can complicate age-appropriate separation in adolescence and young adulthood.

As we move into an era when more and more young adults will know of the hereditary predispositions they carry, the psychological issues surrounding their reproductive decision making are likely to intensify. Preimplantation genetic diagnosis (Avigad et al., 2004) may make it possible to select embryos without the deleterious mutation. Prenatal testing makes it possible to ascertain a child's genetic status before birth, but involves medical complexities and the potential for wrenching decisions about abortion if the child is found to be a mutation carrier. In research to date on adult-onset disorders, it has become clear that decisions about whether or not to have an affected child may be perceived as a judgment about the value of the life of the mutation-carrying parent, complicating the decision making.

HOW IS GENETIC INFORMATION REGARDING CHILDREN DIFFERENT?

When it is adults who are at risk for a hereditary condition, such as hereditary breast/ovarian cancer or Huntington's disease, they make their own decisions about seeking genetic information, about genetic counseling and genetic testing, and about the sharing of genetic information with others in the family. When children are identified as being at high hereditary risk for a disease or disorder, parents or others make far-reaching decisions about the use of that information. Depending on the child's age and the nature of the information, questions may arise about whether the child should be informed about their hereditary risk and when and how that should happen. Separate questions arise about whether the child can usefully and ethically undergo genetic testing and who should know the result. If the decision is made to inform the child or if the child overhears adult conversation about the hereditary predisposition, what they learn may be dependent upon the parent's knowledge of the genetic information and their ability to convey it to others. In fact, we have much to learn about how children in such families come to understand hereditary disease. While there is a small literature on developmental understanding of heredity (Richards, 1994; Silk et al., 2006), much future research could usefully identify the understandings and misunderstandings which are common to children of different ages in families with hereditary disease predisposition and the factors affecting positive psychological adaptation in such children.

When one child in a family is ill, it is normal for the siblings to wonder if they, too, will get the disease. When more than one child in a family has the disease, a child who is spared may feel guilty about *not* being ill and a child who is younger than the ages at which the conditions

were diagnosed in their siblings may think it inevitable that they, too, will develop the disorder. Fanos has written about the experiences of siblings of children with genetic diseases and on the additional potential issues which may occur as a result of the availability of genetic testing (Fanos, 1997). Clearly, children's interest may be acute regarding genetic information about a disease which runs in their family. They may be eager to learn the relevant details about the familial disease or diseases, about how they are transmitted and about the risks to themselves and to their parents and siblings. Significant psychological forces, however, may also interfere with learning about a disease for which one may also be at risk, especially a disease which may have devastated one's family (Richards, 1998). The information source for the genetic information is usually not a genetics professional, but, as noted above, a parent or other relative, with the information sometimes transmitted inadvertently or overheard. Sometimes the transmission of genetic information is from another child in the family, a cousin or sibling. Thus, there may not be an orderly learning process, with questions asked and answers freely given, but, rather, many chances for misperception or misunderstandings.

While there is considerably more openness in talking with children about serious diseases like cancer now than there was even three or four decades ago, hereditary conditions seem more frequently to be associated with secrecy, with one part of the family not wanting another to know or one generation not wanting younger children to be burdened with the information. In such circumstances, it may be difficult for children to be able to ask adults questions they have about the potential risks to their parents, siblings, or themselves. They may, in some families, be told not to discuss the illness of a sibling with a cousin or with friends at school. This can engender a great deal of anxiety and may perpetuate misunderstanding. Access to the Internet may yield answers which may or may not apply to their own risks or may provide outdated information. Genetics is being taught in more advanced ways in elementary, middle, and high schools, but the teaching is not likely to be specific enough to help children or adolescents understand their family's hereditary predisposition.

Children are not usually genetically tested for adult-onset disorders since there is no medical benefit to the child in doing so (Borry, Goffin, Nys, & Dierickx, 2008). Nonetheless, children in families with such disorders may have considerable anxiety about their parents' or their own hereditary risks, as Tercyak and colleagues found in talking with minor children prior to the disclosure of the mother's result (Tercyak, Peshkin, Streisand, & Lerman, 2001) or as reported by parents (Demarco et al., 2008). More research is needed on how children hear and integrate what they are told by parents about hereditary risk, especially when the telling occurs years before there is any relevant action which can be taken to prevent or detect disease early.

Parents make decisions for their children's involvement in genetic or genomic research, as well as for their clinical care. While it is critical that children's DNA be included in biobanks, there are special ethical and legal considerations which must be addressed in this context (Samuel, Ries, Malkin, & Knoppers, 2008). Questions have been raised, for example,

about whether long-term banking of a child's DNA for research purposes necessitates recontact of the child at age of majority for reconsenting in order to continue to utilize the DNA sample. There are also "duty to warn" questions about when and how to inform subjects if significant new data emerge about the implications of their genetic status. While cell phones, e-mail, Facebook, and tracing services increase the opportunities to keep track of pediatric patients as they become adults in order to recontact them, if needed, it remains difficult and expensive to do so and raises ethical issues about privacy rights, what constitutes appropriate recontact, and who should shoulder the responsibility for making such contact.

THE ROLES FOR PEDIATRIC PSYCHOLOGISTS

Pediatric psychologists with their training in cognitive and emotional development and family interaction and impact of illness are ideally suited to offer parents advice about how to help their children cope with hereditary disease and to help children with their concerns about hereditary predisposition or disease. The combination of good training in delivery of clinical service and research means that pediatric psychologists can be key players in the development of the new models of lifelong clinical services for children and families dealing with inherited predispositions. Psychological factors have been shown in adult genetic testing research to be powerful factors affecting the uptake of genetic counseling and testing and the screening and surveillance options recommended to mutation carriers (Antil et al., 2006; Bresser et al., 2007; Meiser et al., 2000). Pediatric psychologists know about the vulnerability of children as they develop their own identities and self-esteem, as they consider how they are like and different from their parents, and how they develop resilience even in the face of family illness and, often, the death of close relatives.

The unevenness of genetic discovery means that pediatric psychologists will have important roles to play in helping to interpret when new knowledge is instrumental and will change treatment options and when it will not. They can help families to avoid testing or treatments which would not yield improvement in the child's status and can help them to understand potential benefits of genetic testing when it is available. Pediatric psychologists can be important resources for parents and children, understanding a great deal about the interaction of cognitive ability, emotional capacity, and family relationships in dealing with complex, rapidly changing, genetic information.

Pediatric psychologists can also be resources for professional colleagues who are eager to know how to speak to children about genetic advances, how to frame requests for experimental genetic treatments, or involvement in genetic research or biobanks. They can also help guide patients to psychotherapeutic services as needed for distress related to hereditary disease.

WHAT COMPETENCIES ARE NEEDED?

In the United States, the National Coalition of Health Professional Education in Genetics (NCHPEG) convened a working group of professionals from many disciplines to write recommendations for the competencies which all health professionals working in genetics should have. The first edition of the Core Competencies was published in 2001 and a revision appeared in 2005 (NCHPEG, 2005). This document details knowledge, skills, and attitudes essential for interacting professionally with families dealing with hereditary disease. Others have adapted the competencies for use by specific disciplines (Guttmacher, Porteous, & McInerny, 2007) including for psychologists (Patenaude, Guttmacher, & Collins, 2002). In general, it is recommended that clinicians working with families with hereditary disease predisposition have sufficient knowledge of the language and concepts of basic genetics, knowledge of the mode of inheritance and disease risks associated with the particular hereditary syndrome or disease, understanding of how genetic counseling helps individuals and families and what its limitations are, and knowledge of whether genetic tests are available for the disease area in which one works. They are also expected to know the nature and limitations of the kinds of test results which are possible from genetic testing. It is also important to know when and how to refer patients for genetic services and how to provide support for those seeking and receiving those services. Also critical is knowledge of whether or how the currently available genetic information translates into personalized surveillance or screening recommendations or targeted treatments (see Table 2).

It is important for all providers, but especially for psychological providers, to be aware of the major emotional, social, and ethical issues which hereditary illness can give rise to. Family dynamics figure

Table 2. Areas of Responsibility for the Pediatric Psychologist in Genomic Medicine

Education	Learn genetic concepts, language; learn to read pedigrees; keep abreast of research advances and clinical translation, targeted genetic treatments, and recommended prevention or risk reduction guidelines. Know local and federal legal protections related to genetic information
Collaboration	Work with genetic counselors, geneticists, pediatricians, pediatric oncologists, nurses, genomic researchers, and ethicists in the care of children with hereditary predisposition to disease. Provide expertise in children's cognitive understanding of illness and their emotional adjustment and coping in relation to hereditary disease. Also expertise on family dynamics and communication and on child and family interaction with medical providers
Ethics	Understand relevance of privacy, proxy consent, assent, right not to know, reconsent, etc., to child and family participation in genetic counseling, testing, research, and treatment
Referral	Know when to make a referral for genetic counseling or testing and how to access appropriate professional services

significantly into care of individuals with hereditary disease predisposition and may interfere directly at times with the care of the patient. Some consider the family the patient in genetic medicine, though the actual implementation of such an approach sometimes involves the provider in ethical conflicts, juxtaposing responsibilities to their patient and to the relatives who need informing. Privacy concerns also necessitate keeping abreast of changing state and Federal laws regarding genetic discrimination and privacy. The passage in May 2008 of the US Federal Genetic Information Non-Discrimination Act helped to reassure families, but state laws will also continue to be relevant (Hudson, Holohan, & Collins, 2008). A database listing US state law regarding genetic discrimination can be found at www.genome.gov/policyethics/legdatabase/pubsearch.cfm.

Cultural and socio-economic issues may figure heavily in family history taking, access to care and attitudes toward hereditary disease. Pediatric psychologists working with diverse populations should familiarize themselves with the cultural understanding of genetics in the particular disease realm and geographic area in which they practice (Halbert, 2006; Armstrong, Micco, Carney, Stopfer, & Putt, 2005; Thomas et al., 2007). Information may come from family members themselves, from religious leaders in the hospital setting or the community, or from review of the growing, albeit small, literature on genetic testing of diverse populations. Cultural concepts such as fatalism (Senior, Marteau, & Peters, 1999) or beliefs about cancer and screening (Liang, Yuan, Mandelblatt, & Pasick, 2004) can complicate the taking of a family history or adherence to targeted recommendations. Understanding of acculturation and its effects are important, as differences in acculturation between generations may imply great variation in beliefs about genetics and medical treatment within the same family (Orom, Cote, Gonzalez, Underwood, & Schwartz, 2008).

A willingness to accept that there is a constant need for updating genetic knowledge in order to treat patients appropriately is critical. Professional education in genetics is widespread to help professionals keep pace with findings from genetic health research. Even those who take courses now to understand modern genetics will find they need to consistently follow advances in their fields, as new discoveries can sometimes dramatically alter what patients with hereditary predispositions are advised to do (Guttmacher et al., 2007).

Basic Genetics Concepts and Tools

To work in a genetics clinic one must be conversant in the basic language of the clinic. Most psychologists studied basic genetics in high school or college biology courses and learned the basics of *dominant* and *recessive* genes. Reviewing these basic concepts will be valuable in remembering the patterns of inheritance that indicate presence of a dominant gene (one in two or 50% of individuals inherit the characteristic) and of recessive conditions (one in four or 25% of individuals inherit the characteristic). These patterns are helpful to geneticists in observing patterns of

disease in very high-risk families with predisposition to monogenic disorders and can help them to consider what pattern of inheritance may be operative. However, these patterns can only be observed to the extent that the condition associated with the mutation is evident. A *mutation* is an alteration from the normal gene structure. *Penetrance* is the risk of developing a disease or condition if one carries a mutation in a particular gene. A penetrance of 100% in a disease gene, like the gene for Huntington's disease, means that everyone who carries that mutation will develop the disease. Penetrance of less than 100% or incomplete penetrance means that some people will carry the relevant mutation, but never develop the disease. It is critical in working with patients with a particular genetic disease to understand the type of inheritance and thereby the risks to them and to their offspring of inheriting the deleterious mutation.

The modern language of genetics involved terms like *single-nucleotide polymorphism (SNP)* or *haplotype* which describe parts of the DNA sequence or of a chromosome. There are also new techniques, such as *genome-wise association studies*, utilizing sequencing data on huge populations to try to isolate small, often rare, genetic differences between affected and unaffected individuals. A useful glossary of genetics terms is available on the Web site of the National Human Genome Research Institute (http://www.genome.gov/glossary.cfm).

However, even knowing basic genetic information about a relevant syndrome or understanding basic concepts will leave many knowledge gaps. Because many cancer predisposition syndromes cause high likelihood of developing multiple cancers, risk estimates often are quite broad for the development of these cancers. Knowledge of the presence of a mutation may not tell you if a particular mutation carrier will develop one or all of the cancers associated with the syndrome. For many syndromes which predispose to more than one disease or form of a disease, research is ongoing to understand the *phenotype–genotype* correlations, i.e., to see if particular mutations are more typically associated with a particular disease or age of onset, but in most syndromes this valuable information is lacking.

Pharmacogenomics is an area of great importance. It relates genetic variation to the efficacy of a drug or to the side effects it imposes on the patient. Personalized medicine is a concept where treatment will not be disease specific, but will be prescribed with an understanding of an individual's genetic makeup and the relevant pharmacogenomics. Knowledge of which patients using a particular drug will do well and which will not could represent huge savings in cost and patient burden in the future (see Chapter 19 in this volume on pharmacogenomics). Pharmacogenomics has already been shown to be useful in the treatment of children with acute lymphoblastic leukemia (ALL; Ansari & Krajinovic, 2007).

Family History Taking and Pedigrees

The family history "has long been regarded as a mainstay" (Guttmacher, Collins, & Carmona, 2004) in caring for patients with hereditary disease. Anyone working in families with hereditary disease needs

to understand how a pedigree is constructed from family history data and needs to be able to read pedigrees which describe the families they serve. A valuable introduction to these topics can be found in *The Practical Guide to the Genetic Family History* by Robin L. Bennett (1999). Learning the symbols for male and female and the basics of how family relationships are represented on these diagrams of family disease history is important in communications with genetic counselors and other genetic professionals. Symbols for death and representation of the cause of death and age at death in classic ways are important to learn. There are also classic ways to represent the presence of various diseases on pedigrees as well as ways to represent miscarriages, divorce and remarriage, and other relevant life events.

Reviewing pedigrees with genetics colleagues can be useful in understanding the central role certain aspects of family history can have in diagnosing hereditary disease. The need to constantly update family histories to include all recent diagnoses among family members will also be important, since it is often only with time that the family disease pattern comes to clearly represent a hereditary syndrome (Garber et al., 1991). Review of the family history can also clarify which family members need to be advised about the genetic information that is known. Other family history tools can be found at US Surgeon General's Family History Initiative (http://www.hhs.gov/familyhistory/), the American Medical Association site for prenatal, pediatric, and patient family histories (http://www.ama-assn.org.ama/pub/category/2380.html).

Genetics Resources

Finding appropriate genetic services for one's patients is a critical skill for any professional caring for patients with hereditary disease. It is also helpful to have trusted sources for genetic information, both to update one's own knowledge and to provide patients with explanatory materials. An excellent list of genetic resources available for the clinician on the Internet can be found in an article by Ulmann and Guttmacher (2008). This article also has links for finding trained geneticists and genetic counselors, including links for the American College of Medical Genetics site ("Find a Geneticist" at http://acmg.nt), the site for the National Society of Genetic Counselors (http://www.nsgc.org/resourcelink.cfm), and the NCI site for locating cancer genetics specialists (http://www.cancer.gov/search/genetics_services/).

Ethical Issues Concerning Children and Genetic Testing

It is important for pediatric psychologists to have a broad understanding of the ethical issues which relate to children in the context of genetic testing or genomic research. A number of professional organizations have published guidelines about children and genetic testing. A recent review found 27 such guidelines or positions papers from US and international professional societies, bioethics, advocacy, or advisory groups (Borry, Stultiens, Nys, Cassiman, & Dierickx, 2006). While there was general

consensus about medical benefit to the child being the fulcrum differentiating approval versus disapproval of genetic testing in childhood, the authors illustrate the difficulties in practical application of this seemingly straightforward mandate. They also discuss ambiguity in guidelines about who should decide about the genetic testing of a child with a hereditary childhood-onset disorder when there is no treatment or prevention benefit to testing, other than possible psychological effects. Among the guidelines surveyed, cultural differences were evident, with US guidelines typically recognizing age of majority (age 18) as the point at which children, rather than parents, should be asked to provide consent, while British guidelines gave decision-making authority to children between 16 and 18 with appropriate maturity. French guidelines felt decision making should be in accordance with the child's maturity (age unspecified), and Danish guidelines gave children as young as 15 such authority. Questions to what constitutes "maturity" in this context and what knowledge is necessary for decision making are areas of fruitful future research. Differentiation between adult- and childhood-onset disorders is not always made in the guidelines and even when present, may not always reflect practical situations. Huntington's disease is often cited as the adult-onset disorder for which genetic testing should be delayed until adulthood, given the lack of treatment. However, 5–10% of Huntington's disease occurs in childhood, some cases as early as age 9 (Aubeeluck & Brewer, 2008), raising issues about childhood testing in such families.

Generally, the guidelines ascribe legitimacy to the testing of children when there is medical benefit to the child if their genetic risk status were to become known. One of the clearest examples is familial adenomatous polyposis (FAP), a hereditary colon cancer which affects young people. In families with FAP, it is recommended that children as young as 10 get annual colonoscopies, since the pre-cancerous sign of the start of the disease is the formation of many colon polyps. Surgery to prevent colon cancer may be done as early as age 16 to remove the parts of the colon where large numbers of polyps have formed (Lynch, Lynch, Lynch, & Attard, 2008). However, in FAP families where the risk of inheriting the deleterious mutation is 50%, genetic testing to determine which children are actually mutation carriers will also identify the 50% of children who do not need to undergo these invasive measures. Hence, genetic testing is clearly in the best interest of children in FAP families. In families with cystic fibrosis, genetic testing can sometimes help clarify equivocal sweat tests, although, due to the range of possible mutations, there are still instances where neither sweat testing nor genetic testing provides the desired clarification (Mishra, Greaves, & Massie, 2005).

The professional guidelines have typically also recommended that when there is no immediate medical benefit to the genetic testing, such as might be the case in clinical genetic testing of children for adult-onset conditions, like *BRCA1/2* predisposition to hereditary breast/ovarian cancer, that testing of children and adolescents be discouraged or not allowed. However, there may be reasons why genetic research on late-onset disorders may involve the genetic testing of children and professional groups,

including the American Academy of Pediatrics (2001), have given support to research in this context.

Ethical Considerations in Pediatric Clinical Research

There are guidelines about children's involvement in clinical research, but few specifically deal with children in genetic research (Patenaude et al., 2006). Clinical research is differentiated from clinical practice by the experimental nature of the approach. As such, it is likely to be much more uncertain in its outcome and may involve tests which do not have the same high level of clinical validity which are used in clinical practice. Clinical genetics typically mandates that individuals seeking genetic testing undergo prior genetic counseling so that they understand the results and their limitations and can, thus, make an informed decision about the testing. Children are likely to be involved in clinical genetic or genomic research because they are members of high-risk families, in studies seeking the genetic origins and/or environmental triggers for pediatric or adult diseases and in studies of potential preventive interventions for later-onset disease. There is increasing interest in risk factors of childhood and adolescence for late-onset disease (Daniels & Greer, 2008; Toprak et al., 2008; Freedman et al., 2008). In clinical research, results are not typically given to participants, as the meaning of the result may be unclear or invalid. There may be additional concerns about the question of whether giving a genetic test result to the parents contravenes the child's right to possibly not ever know their genetic risk status, sometimes discussed as the "right to an open future" (Davis, 1997).

The line between clinical research and clinical practice can blur sometimes as genetic research progresses and there can be dilemmas which arise as one tries to merge individual rights of research participants or clinically tested individuals with those of their family members. An interesting example of such a dilemma involves ongoing genetic research in Newfoundland on arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5). This condition causes high rates of sudden cardiac death in males as young as in their teens and in females as early as in their late twenties (Pullman, Hodgkinson, Dicks, & Brunger, 2008). In the absence of treatment, 50% of males die by age 40 and 80% by age 50, with corresponding lesser risks for females of 5 and 20% by age 50. While a gene, *TMEM43*, has very recently been found which appears to be responsible for ARVC5 (Merner et al., 2008), prior to this discovery, DNA testing for this condition was considered research. However, due to the severity of the condition and the frequent lack of any cardiac symptoms prior to sudden cardiac death, individuals were given intermediate research results and implantable cardiverter defibrillator therapy was initiated in individuals who had haplotypes associated with the condition. Dilemmas arose for the researchers when some subjects refused to get their research results, preventing other at-risk relatives from being informed of their risks, and, in at least one case, resulting in lack of treatment for a young man who suffered sudden cardiac death before age 30. The researchers' ultimate response was not to include individuals in the research genetic

testing unless the individuals promised to get their test result (Pullman & Hodgkinson, 2006). Genetic counseling was also provided to those at risk who participated in the study, detailing the limits on the knowledge currently available. The authors suggest that the limits between research and clinical care in genetics may be ambiguous and that "more nuanced understanding of the relationship between genetic research and clinical practice is essential as we move forward in this regard" (Pullman & Hodgkinson, 2006).

Biobanks and Children

The relative rarity of hereditary disease in children makes the banking of pediatric tissue from children in hereditary cancer families especially valuable (Balaguer et al., 2006). There are, however, a great many ethical, legal, and social issues which the long-term banking of DNA samples gives rise to (Haga & Beskow, 2008). Pediatric psychologists will be valuable members of oversight teams dealing with issues about understanding of consent documents by parents, need for reconsent at age of majority and potential reconsent for updated medical information, allowable use of the samples, etc.

CONCLUSIONS

While pediatrics lags behind adult medicine in the integration of genetics and genetic testing, there remain many interesting, challenging dilemmas and fields for research for the pediatric psychologist interested in a career focusing on this emerging area. Entry into such a field requires groundwork for the pediatric psychologist (as for many other professionals as well). This includes grounding in the basics of the new genetics, the psychosocial ramifications and ways in which cultural factors affect such ramifications, and study of the ethical dilemmas which may arise in the course of pediatric practice and research involving children. Psychologists who keep abreast of their own rapidly changing area of genetic patient care, including an awareness of the international literature and of the range of approaches to dealing with similar genetic issues, will help insure openness of thinking in consideration of issues raised by the new genetics. These well-informed psychologists can also help in the development of guidelines which specifically address issues of children's involvement in genetic medicine. Collegial discourse with research and medical professionals, with bioethicists, genetic counselors, parents, and with advocacy groups will also help insure exposure to new challenges. Pediatric psychologists can utilize their own rich trove of understanding of children's emotions and development to find answer to questions about the translation of genomic findings into clinical medicine. There is much research to be done on the family and social impact of genetic disease, on the ways in which different generations approach, speak about, and integrate this new knowledge, and on how different genetic circumstances (monogenic disorders versus more complex gene–gene or gene–environment relationships)

affect the child, the parent, and the professional in utilizing the genetic information. There is certainly much research needed on how the nature of the disorder (medical versus psychiatric) affects use of genetic information and on social views of hereditary conditions in children. Pediatric psychologists can do much to define how childhood itself is affected by new genetic knowledge. These and many other questions can fill the careers of many future generations of pediatric psychologists willing to pay the price of upgrading and constantly reviewing their knowledge of hereditary disease and their understanding of the dilemmas which affected families face. Pediatric psychologists have much to contribute to research evaluating the impact of genetics into the practice of pediatrics and to creation of informed policies to appropriately guide children, families, and professionals involved in genetic research and clinical care.

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Public Health Genomics

SUZANNE C. O'NEILL

This volume has provided a broad and comprehensive review of psychosocial and behavioral concerns of children, adolescents, and their families in the context of genomic medicine and health care. In addition to considering current applications for genomics in this population, including prenatal and newborn screening and carrier testing, it also tackled the major issues involved in the future translation of genomics to primary prevention among young and healthy individuals.

This final chapter focuses on current and potential future research trends and clinical applications of genomics impacting pediatric populations, how the expanding knowledge of genomics impacts pediatric public health, and how social and behavioral scientists contribute to these efforts. Such considerations fall under the umbrella of *public health genomics* and range from gaining a better understanding of disease biology to whether and how risk information can be provided to motivate behavior change (Khoury et al. 2008). This chapter introduces public health genomics and covers four central issues that social and behavioral scientists should understand when considering these issues in the context of pediatrics. These include (1) the questions of whether, when, and how to disclose genomic risk information to minors; (2) the related challenge presented by the need to further build research infrastructure and how to provide informed consent/assent to minors; (3) the growing recognition of the significant impact of early environment on gene expression, often discussed within the context of the growing interest in the *D*evelopmental *O*rigins of *H*ealth and *D*isease (DOHaD) and specifically epigenetics and epigenomics; and (4) adding improved phenotypes and exposure measures with more powerful genomic tools as a means of potentially strengthening genotype–phenotype associations. Stronger and more consistent associations would provide more confidence in whether genomic information is reliable and/or useful enough to disclose to minors and their families. This confidence necessarily and directly impacts the questions related to the disclosure of genomic risk information. Therefore, rather than seeing

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these as four separate and unique challenges, the topics discussed in this chapter should be viewed as a set of interrelated areas to be considered simultaneously to move the field forward.

These topics are addressed from a developmental life span perspective, encompassing the prenatal period, early childhood, teenage, and adult/family issues. These life periods are cyclical, as opposed to a finite continuum, because of the impact that parents and other caretakers have on children, from the prenatal period forward. This chapter concludes by applying some of these considerations to examples from recent pediatric lipid screening and management guidelines and interpreting how genomics may contribute to alleviating this important public health problem.

WHAT IS PUBLIC HEALTH GENOMICS?

Public health genomics is the study and application of knowledge about the human genome and its functions. This includes domains such as how the genome interacts with the environment and the effect of integrating genomic information into interventions and therapies to improve population health and lessen disease states (Burke, Khoury, Stewart, & Zimmern, 2006). Public health genomics reaches across numerous population science fields and domains, from epidemiological studies of disease susceptibility to intervention research that integrates this information to change health behavior for health promotion or disease prevention (Khoury, Davis, Gwinn, Lindegren, & Yoon, 2005). These diverse disciplines must be engaged in order to translate genomics from discovery to public health impact (Agurs-Collins et al., 2008). Ultimately, clinical studies of health behavior and health education interventions could determine whether integration of genomic information has clinical utility and/or impact on population health (Burke, 2009). Current public health genomics priorities, as set by the Center for Disease Control and Prevention's (CDC) Office of Public Health Genomics, include conducting population-based genomics research, supporting the evaluation of genetic tests, and translating genomic knowledge (Khoury et al., 2009).

As detailed in this volume, there are numerous challenges to be met before we can begin to know what impact genomics has on population health. Unfortunately, much of the work in public health genomics has been aimed at adult populations to date. Indeed, most epidemiological studies in this area employ adult populations, both due to the need to link genetic findings to manifest disease and due to practical and philosophical issues of involving children in medical research and genetic research specifically (Almond, 2006; Ross, 2003). This contrasts with the field of medical genetics, where pediatrics has played a rather critical role. For example, early advances in genetics positively impacted the health of children with metabolic disorders who would have otherwise died or had significant health challenges (Rimoin & Hirschhorn, 2004). If one of the goals of public health genomics is to integrate information into disease prevention interventions, notably primary prevention, then greater

consideration must be paid to reaching out to pediatric populations in a research context.

Engaging pediatric populations, their families, and providers could have multiple benefits. Many health risk behaviors that contribute to increased morbidity and mortality in adulthood either start or escalate during adolescence (Eaton et al., 2006). Risky health behaviors can also begin even earlier. For instance, evidence indicates that energy-related health behaviors predisposing to obesity cluster or co-occur (Sallis, Owen, & Fotheringham, 2000). These clusters can emerge as young as 2 years of age (Gubbels et al., 2009). Even though these behaviors are not linked to co-occurring obesity at this early age, it underscores the impact of early intervention. Once poor health habits are formed, they take a significant toll on personal and collective physical, social, and economic well-being (Chaloupka & Johnston, 2007). Changing these behaviors can prove challenging in the adult phase of life (Prochaska, Spring, & Nigg, 2008). If knowledge of genomic information is to impact public health, consideration must be given to integrating this information into pediatric health. With these points in mind, there are several considerations that need to be taken into account regarding the use of young populations in the development of our knowledge base and also the application of this knowledge in intervention research.

DISCLOSURE OF GENETIC RISK INFORMATION AND ASSOCIATED HEALTH DECISIONS

Clinical practice guidelines discourage pediatric genetic testing for adult-onset diseases. Though some guidelines acknowledge that there may be psychological benefits to knowing risk status as a means of reducing uncertainty, the majority of guidelines that distinguish adult-onset diseases from child-onset diseases state that testing is only recommended when an established, effective, and important medical treatment can be offered during childhood or when testing prevents, delays, or eases the disease itself, or its symptoms, from manifesting (Clark, 1994; American Society of Human Genetics, 1995; American Academy of Pediatrics, 2001; American Society of Clinical Oncology, 2003).

However, many young people grow up with the knowledge that a disease is present in a family member and that they, too, may be at risk. There has been little research to date that has focused on how young people acknowledge or deny "growing up" with genetic risk information. Much of the discussions to date have focused on respect for the child's future autonomy in the decision-making process and the appropriate age to offer testing. Yet, consideration could be given to the preferences of minors themselves about favored ages for informing about genetic risk status and offering carrier testing.

There are two interrelated themes in this area. On the one hand, more work is needed to establish the risk/benefit ratio and related protections of this vulnerable population in genomic research and the interplay between research-based and clinically based genomic discovery and its affects on

children. On the other hand, there is a developing literature about family communication and risk communication as it relates to test result disclosure and how the impact may vary depending on the developmental timing of this risk communication. A better understanding of how the awareness of disease risk impacts a young person's developing self-concept directly informs the above risk/benefit ratio and the appropriate level of protection for minors participating in genomic research.

Research on families facing risks from monogenic disorders, such as fragile X syndrome, provides a useful window into how young people cope with potential future health risks. Fragile X syndrome is the most common heritable form of moderate mental retardation. An X-linked triplet repeat disorder, it is diagnosed by the presence of a mutation in the *FMR1* gene. The disease has a variable phenotype depending on the number of repeats present. Almost all males and about half of females who inherit a full mutation will develop fragile X syndrome, resulting in a range of cognitive and behavioral symptoms. Women who possess a premutation are at risk for fragile X-associated tremor/ataxia, primary ovarian insufficiency, which can impede fertility, and for having a fragile X-affected child. Therefore, this information is important for young women of childbearing age.

In a series of qualitative interviews with young women with a family history of fragile X syndrome who either knew whether they were carriers or non-carriers or who had not been tested (McConkie-Rosell, Heise, & Spiridigliozzi, 2009; Wehbe, Spiridigliozzi, Heise, Dawson, & McConkie-Rosell, 2009) examined the process of learning about their carrier status and the impact this had on their psychosocial development: 57% of young women learned that fragile X was an inherited disorder as well as the possibility of being a carrier before the age of 14 and 45% had been tested and knew their status before this time.

The majority of these women cited the preteen or teen years as being most appropriate to learn about the possibility of being a carrier, citing intellectual, physical, and social maturity as reasons that impacted this decision. There was wider variation across the sample regarding the best age to be tested, ranging from early childhood upward, with many being either unable or unwilling to give a response, generally citing an individual's autonomy in this decision as a reason for not offering a specific age. One-third of the sample who had been tested believed that parents had the right to choose the timing of having their daughter tested, whereas none of the women who had not been tested advocated for this. When asked if they would change anything about how they learned of their risk, 68% said they would not change anything. Of those who would change something, they offered that they wished they had learned earlier, that the knowledge had been disclosed in stages, that they had been more involved in the process, that they had been better informed, and that they had paid more attention when being told about their potential risks and the implications. Overall, girls who had been tested and knew their actual carrier status were more likely to report an open communication pattern than girls who knew only that they were at risk.

This work provides a starting point from which to consider the multiple implications of genetic testing of minors for the purposes of primary prevention, thinking particularly about risk for common chronic disease. Test result disclosure is impacted by the developmental evolution of understanding of disease risk, as well as the appropriate age to engage minors in these conversations. For instance, a very young child may know that there is a difference in his/her family due to a certain disease; it does not need to be explained. Despite this awareness, he/she may neither need nor be able to process an explanation of the disease, future risks involved, and implications for the child and other family members.

Fragile X is one of many monogenic disorders that is physically apparent, thus presenting itself to the child from an early age. The difference between this and other diseases is that there is no way to hide this risk – it is always present. To move this to the setting of common chronic disease, there are a number of diseases that a child may be less aware of as he/she matures. There are some physical and behavioral conditions that are more obvious, due to either overt manifestations of the condition or monitoring that must occur in the home and, therefore, becomes part of the family's life. Some examples of these would include obesity and diabetes. For instance, from an early age, a child is aware of overweight status of oneself or one's family members. This awareness can begin to have an impact on their long-term well-being (Cave, 2009). In contrast, other conditions, such as hypertension and certain cancers, are less noticeable. The implications of learning one's risk for disease may vary based on whether this risk fits with what one observes in one's family, and is thus expected, and whether this risk is novel and must be learned about.

Conversations that health-care providers have with minors about genetic risk and its implications may best be done through several consultations over time. This approach is similar to the pediatric model of care in which a provider has a relationship with a patient and his/her family that unfolds over time. These conversations could perhaps better integrate the child's developmental level and the family's strengths. This is in contrast, however, to most other medical models, including the typical genetic services approach, which involves one or a limited number of interactions that normally do not allow for such an understanding to unfold over time.

There are a number of ways to address children's and families' communication needs. New technologies could be used to bridge this gap in practice structures. These technologies could be a means to reach teenagers, allow their providers to learn more about what teens think about these issues, and be a means to extend the conversation about risk beyond the one-time encounter that occurs during an annual wellness checkup or an appointment with a genetic services provider. New technologies also allow for affected minors to access information and support of others in their community. One example of this is the web-based resources provided by the National Marfan Foundation. Such methods could be used to normalize identity development and provide important links to affected peers and social networks, which could positively impact identity development. Rather than foreclose an identity, knowing one's risk

as a minor may allow for this information to be integrated into their sense of self in a healthy way, rather than having to adjust to this information as an adult or all at once. Similar portals could be used as settings for health behavior change interventions if further research indicates that they are effective.

The types of conversations one would have with the child also evolve as the child becomes older and more cognitively aware and with additional life experience. A recent review of family communication about inherited genetic conditions (Metcalfe, Coad, Plumridge, Gill, & Farndon, 2008) found that open communication facilitated psychosocial adaption to genetic risk information. Children from families in which information was not shared or were marked with more closed communication styles expressed more upset, and also more frustration, about secrecy. Adult children who learned of their risk after being "protected" from the parents about such information reported feeling resentful of this secrecy and often had incomplete understandings of the disease and associated risks. This closed approach also does not allow parents and children to cope with the emotions associated with their genetic condition. The metasynthesis suggested that parents need additional help in learning how to communicate with their children about genetic conditions. Yet, there is often little assistance for communicating complex risk information and addressing associated emotional issues. Parents might benefit from communication training regarding how to discuss these topics with their children. Based on their review, Metcalfe et al. (2008) suggest that future work incorporate family communication theory and that this research should go beyond exploring the appropriateness of testing of minors to consider wider implications of living with a genetic condition. Multiple chapters in this volume highlight the importance of including the family system in future research. Indeed, families may benefit from communication training, as families who have not dealt with such issues effectively in the past may face broader and more persistent difficulties with communication.

Edwards et al.'s (2008) recent systematic review of interventions to improve risk communication in clinical genetics found that interventions achieve some benefit, mostly in the area of cognitive outcomes, such as improved knowledge and more accurate risk perceptions. There is less clear benefit at this time for outcomes such as affect, behavior, or health status. They suggest that as the scope of clinical genetics broadens to include many conditions that incorporate the clear contribution of genes and environment, it will be important to enhance and evaluate genetic risk communication in this arena. They also propose that trials are needed regarding how to use decision aids and other tools as adjuncts to counseling for emotional support, even prior to meeting with a clinician, and to understand the effective components of such interventions.

Finally, most of our research on how individuals will react to genetic risk information comes from testing for high-risk, high-penetrant mutations. Individuals who are eligible for this testing start with the notion that they hail from an at-risk family. In contrast, when considering testing for common disease, many people would not enter testing with a strong family history of a particular disease. Therefore, they may come with an

assumption of health. This may have an impact on how information is received and acted upon (if at all). We must understand this process in order to apply genomic information to prevention in healthy individuals without strong family histories of disease. One option to begin this process is to survey healthy adolescents to examine their attitudes and preferences. Some examples include studies of teenage carriers of Tay–Sachs disease and hemochromatosis. Another option is to examine parents' opinions of testing for their minor children or how testing for their own risk might impact the health of their children.

Testing for common variants associated with multiple disease risk has been done in a limited number of studies. One example of this is the Multiplex Project, led by a combination of researchers from the National Institutes of Health, Group Health Cooperative, and Henry Ford Health System. The purpose of the study is to investigate the interest level of healthy, young adults in receiving genetic testing for eight common conditions, including type 2 diabetes, coronary heart disease, high cholesterol, high blood pressure, osteoporosis, lung cancer, colorectal cancer, and malignant melanoma. The study is also examining how people who decide to take the tests will interpret and use the results in making their own health-care decisions in the future.

PROVIDING INFORMED CONSENT/ASSENT AND THE NEED TO BUILD OUR KNOWLEDGE BASE

To begin to build our genomic knowledge base, we must better engage adolescents and their families in this research. But as with other vulnerable populations, informed assent/consent is paramount. Following on the previous section on genomic risk communication, informed consent must take into account how children and adolescents interpret and apply risk information and how this relates to their (and adults') ability to provide informed consent. Prior to considering studies that would test minors to assess their responses to testing, work is needed that assesses their understanding of risks and benefits in the absence of testing. Specifically, adolescents may have difficulty imagining the future implications of testing and of how risky behaviors impact future health states. This leads to a number of important questions: What does the education level need to be to integrate this information into systems that affect children, such as schools? An obvious point for integration is high school biology, but there may also be other opportunities within in the curriculum to expand the genetic literacy of young people. Similarly, there have been efforts to integrate financial education into school curricula in developmentally appropriate ways (Suiter & McCorkle, 2008), including discussions of financial decisions and their possible consequences. The fundamentals of risk communication, including the understanding of probabilities and immediate versus long-term gains, are similar in each of these applications. The need for such education has been made clear in recent years when considering our future physical and financial health. These general concepts could be better integrated into secondary education curricula.

A major challenge is building research studies that gather the data we need to answer such questions from a developmental perspective is the need to provide appropriate assent/consent. Most existing data sets are not prepared to answer gene × environment (G × E) interaction questions at this time, particularly from a developmental perspective, but this is changing with the advent of the National Children's Study. This effort, led by National Institutes of Child Health and Human Development and Environmental Health Sciences, the Centers for Disease Control and Prevention, and the Environmental Protection Agency, has a number of features that would allow the field to begin to address such issues.

The National Children's Study will draw on over 10,000 participants from varied geographical locations, backgrounds, and family structures, all to better reflect the diversity of environments in the United States. Second, environment is, indeed, defined broadly. Data are being gathered about the natural and man-made environments; biological, chemical, physical, and social surroundings; and behavioral, genetic, and cultural/family influences that impact children's health and development from before birth through age 21. This ensures that variables are not being considered in isolation. It involves a public–private partnership, involving Federal, state, and local agencies, academic researchers, and private companies, working together to develop comprehensive, unbiased data. The results are made public throughout the study, allowing for new questions to be asked as knowledge accrues.

Research infrastructures such as this, when combined with teams of researchers who ask questions from a transdisciplinary perspective that will take advantage of what these and other data have to offer, hold promise for completing many of our unknown areas related to gene–environment interactions from a developmental perspective. The determination of whether and how we can ethically engage pediatric populations in genetic research will facilitate the research discussed in the next two sections: (1) the impact of early environment on gene expression and health and (2) the improvement of phenotypes and exposure measurement in genomic studies.

IMPACT OF EARLY ENVIRONMENT ON GENE EXPRESSION AND OVERALL HEALTH

One of the many questions that the National Children's Study will address is how genes and environmental factors exert their influence and interact during early development to impact outcomes. We have known the importance of adverse early environments on later health outcomes for a long time, but the mechanisms by which these outcomes occur, and therefore the points at which we should intervene, have been more elusive.

Further, the growing area of DOHaD and epigenetics/epigenomics is becoming just as important as the study of genes themselves. Basic research that combines neurobiology, genetics, and family environment to predict maladaptive outcomes allows for the potential of earlier and

more innovative interventions. For instance, a multifactorial intervention designed to target several pathways that contribute to the development or maintenance of a disease may be more effective than an approach that targets only one of these vectors.

DOHaD research has included the study of epigenetic phenomena for many years and continues to grow. Epigenetics, originally defined to describe the study of "the interactions between genes and their products which bring phenotype into being" (Waddington, 1957), has expanded to include the broader concept of the study of heritable changes in gene expression that are not caused by changes in gene sequence (Cutfield, Hofman, Mitchell, & Morison, 2007) and, more recently, heritable changes in gene expression potential (Jaenisch & Bird, 2003), or how environmental experience enters the genome (Feinberg, 2008).

One example of work in this area focuses on methylation, the addition of a methyl group to the nucleotide cytosine in the genetic code of individual cells: methylation is passed on to daughter cells through cell division, and DNA methylation may have a role in maintaining chromosome stability and gene silencing. These impacts appear to occur at two main points, gametogenesis (preimplantation) and in the late-term fetus/early neonate. Significant research has been conducted in animal models and in using retrospective human data to support the impact that environmental circumstances (such as early nutrition, e.g., Roseboom et al., 2001; Gluckman & Hanson, 2007) and the stress response (e.g., Weaver et al., 2004, 2005) have on later health outcomes.

A recent meeting report of the Third International Congress on Developmental Origins of Health and Disease (Gillman et al., 2007) pointed to a number of emerging themes in this area. These include (1) how postnatal influences modulate intrauterine programming, such as how infant weight gain may predict adult obesity and other chronic diseases; (2) how the emerging epidemic of obesity in the developing and developed world, including the impact of both the under- and the over-nourished fetus, combine with postnatal environmental factors to lead to higher rates of obesity and related diseases; (3) the impact of environmental toxins, ranging from bisphenol A to maternal smoking, on development; and (4) how epigenetic phenomena may explain observed outcomes, such as how maternal diet may impact offspring outcomes.

While this work could lead social and behavioral researchers to design interventions to enhance prenatal nutrition that would impact the fetal environment at critical time points, Gluckman and Hanson (2007) suggest this work be implemented with a large dose of caution. Previous studies that have tried to apply nutritional supplementation during pregnancy, with the clear and predictable expectation for positive outcomes, were unsuccessful. Intervening in infancy or early childhood may be a more effective option in this regard, though would potentially miss impacting those compromised by preterm birth and other complications. The authors also suggest that any such intervention be informed by a sound understanding of basic science to adequately answer questions such as what type of intervention, to whom and when during the life span it should be applied, and for what specific outcomes. Answering each of these

important questions will require more research and ultimately could allow us to capture this important phenomenon.

IMPROVED PHENOTYPES AND EXPOSURE MEASUREMENTS

One of the primary and well-founded criticisms of the disclosure of genetic information related to common disease risk is the lack of precision and strength in these risk estimates and current understanding of G × E interactions (Ioannidis, Thomas, & Daly, 2009; Manolio, 2009; Henrikson, Bowen, & Burke, 2009). These estimates could be improved through genetic methods, better assessments of environments, and refined definitions of disease. As mentioned throughout this volume, one of the many reasons for the lack of precision when characterizing risk associated with complex chronic disease and neuropsychiatric disorders is the multifactorial nature of disease and the classification system used for neuropsychiatric disorders, as well as poor and inconsistent measures of environmental exposures in existing data sets. One way to potentially improve upon these associations may be to make phenotypes more refined and precise. For example, rather than looking at associations with diseases or complex traits broadly, one could look at associations with a marker of a particular disease (Swanson et al., 2007; Acosta et al., 2008).

In their groundbreaking work in neuropsychiatric genetics (Gottesman & Shields, 1972, 1973) expanded on John and Lewis' (1966) work in insect biology to arrive at the concept of "endophenotypes." These were defined as internal phenotypes discernible through a "biochemical test or microscopic examination" and include neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, and neuropsychological aspects of a condition (Gottesman & Gould, 2003). Using endophenotypes allows for the identification of specific traits or aspects of a disorder, such as symptom clustering, rather than identifying the genes associated with a complex disease or syndrome. Fewer genes are likely to be associated with these discrete traits than if one were to compare individuals with and without a particular disease, with its many causes and features. This allows for potentially more robust genotype–phenotype associations. There are a number of examples of this approach, such as the identification of genes associated with long QT syndrome (Keating & Sanguinetti, 2001) and the role of dopamine pathway genes and ADHD (Swanson et al., 2007). The use of endophenotypes and other methods to refine disease phenotypes also promotes a better understanding of the underlying biology of disease.

Examining the genetics of these traits or features, as opposed to those of complex disorders themselves, is a promising approach that has gained ground in recent years. Future research in this area must be somewhat cautious, however, as these endophenotypes may not be genetic, but rather environmental, epigenetic, or a combination of these (Gottesman & Gould, 2003). Gottesman and Gould (2003) adapted suggestions offered by others in neuropsychiatric genetics (Gershon & Goldin, 1986; Leboyer

et al., 1998) to offer guidelines for selecting endophenotypes to examine in genetic studies, including the following: (1) the endophenotype must be associated with the disease in question, (2) it must be hereditable, (3) primarily state independent, such that it does not wax and wane with symptoms severity, (4) must co-segregate within families, and (5) should be found in unaffected family members at rates higher than in the general population.

In addition to defining endophenotypes, other methods for refining the definitions of disease include statistical methods to better distinguish behavioral traits shared with commonly comorbid disease. One example of this is the use of latent class analysis for ADHD and comorbid conditions, such as Conduct Disorder and Oppositional Defiant Disorder (Acosta et al., 2008; Jain et al., 2007). This method allows for both inclusion of information about comorbidities, as well as milder, but impairing phenotypes that would not meet the threshold for diagnosis under current classification criteria (e.g., American Psychiatric Association, 2000). This approach has led to the identification of several markers associated with ADHD and other comorbid disorders (Jain et al., 2007), potentially leading to more effective interventions.

Another way to increase the precision of estimates is to use more precise measures of phenotypes and environmental exposures, including behaviors, in genomic studies, as well as more standard measures across studies in order to facilitate comparison and combination of findings. The PhenX Project, a combined effort of RTI International and the National Human Genome Research Institute, serves as an interesting example. The goal of this effort is to develop a toolkit of standard measures. Domains included span diseases and conditions, lifestyle factors and anthropometrics, and environmental and medicinal exposures. Thus far, the Steering Committee of this group has determined that the domains to be covered in this project would be those that are clearly defined, are of significant research and public health interest, broadly applicable as an outcome, covariate or both, can expect measures to be accepted by the relevant research community, and are a reflection of broad scientific expertise (PhenX, 2009). Work began with examination of measures of demographics, alcohol, tobacco, and other substance use, and anthropometrics, such as pregnancy weight gain, and maximum adult height and weight. Soon, more domains, including cardiovascular factors and nutrition, are expected to be added. More precise associations and a better understanding of how environmental factors impact both genomic expression and health will facilitate social and behavioral research in this area.

The need for accurate environmental assessment takes us back to the earlier sections of this chapter – the need to determine how to engage minors in this research and what and how to tell them about genomic information. Parents may be the best source for many measures of early environment, such as diet, physical activity, exposure to toxins such as secondhand smoke, and stressors in the family and community environment for young children. But as children age into adolescence, they can become reporters to their own environments and may be more beneficial when the focus of investigation is on risky behaviors such as

substance use and abuse or sexual activity. Likewise, as they mature, they must become involved in the reporting of psychiatric symptomatology. Thus, we must confront issues related to engaging minors in genetic and genomic research. Social and behavioral scientists can provide unique contributions to this process by applying their expertise in diagnostic assessment and behavioral measurement, including assessments of children's capacities of mental understanding and competence at differing ages.

An Example: Pediatric Lipid Screening

This chapter has addressed related questions of the method and impact of genomic risk communication, related challenges of providing informed consent/assent to minors in the context of genomic research, and new avenues for G × E research. These areas hold promise and underscore issues surrounding communication and assent/consent. These issues can be applied to the example of pediatric lipid screening. Recently, the American Academy of Pediatrics changed their guidelines regarding lipid screening and intervention-related cardiovascular health (Daniels & Greer, 2008). Retirement of the previous guidelines came after a combination of factors, including the mounting obesity epidemic, clearer evidence regarding the safety and utility of pharmacologic agents, and data demonstrating the development of atherosclerosis in childhood as a marker for later disease. The most current recommendation is to screen children and adolescents via fasting lipid profile under the following conditions:

- Those with a known family history of dyslipidemia or cardiovascular disease before the age of 55 in men or 65 in women.
- If family history is not known, screening is recommended for those showing other risk factors, including overweight, obesity, hypertension, cigarette smoking, and/or diabetes mellitus.

For such children, screening should take place after age 2 but no later than age 10. Among those who are overweight or obese and demonstrate high triglycerides and/or low HDL concentration, a weight management intervention is recommended. This includes changes in both diet and physical activity. For those over age 8 with high LDL concentrations, pharmacologic intervention is recommended, particularly if there is a strong family history of cardiovascular disease and the presence of other risk factors.

The primary purpose of the guideline is the early identification of at-risk individuals. There are several monogenic forms of severe hypercholesterolemia that are in particular need of early identification and treatment. The best known of these, familial hypercholesterolemia (FH), is a disorder of LDL cholesterol metabolism caused by mutations in *LDLR*. Mutations in other genes, such as *APOB* and *PCSK9*, have been found to have similar effects. Identified FH-causing mutations in individuals have clinical implications for other family members (Rahalkar & Hegele, 2008). Homozygous FH is rare (1 in 1 million) and easily diagnosed early in life

through the presence of planar xanthoma and early-onset atherosclerosis. In contrast, the World Health Organization estimates the incidence of heterozygous FH to be 0.2% (1 in 500) in the United States, making it one of the most common monogenic conditions. Untreated individuals with heterozygous FH have an increased risk of early myocardial infarction and death before the age of 60. This risk is substantially mitigated by aggressive treatment. However, it is estimated that only ~5% of affected individuals have been diagnosed and <10% of diagnosed FH patients are adequately treated. Definitive diagnosis is made through genetic testing (van Aalst-Cohen et al., 2006), though validation of less expensive clinical markers is also under study (Benlian et al., 2009).

Genome-wide association studies have made significant progress in generating a number of genetic variants associated with lipid levels, as well as environmental modifiers of genetic effects (Manolio, 2009). Yet, even with this recent progress and the increasing number of identified loci, these markers still explain only a small part of the variance in complex disease. Further, these markers require additional validation and are not ready to be used in clinical settings. Limited research to date suggests that children with FH provide a better model for performing genotype–phenotype associations than their adult relatives. This is due to the fact that adults with FH have a long history of other lifestyle factors and often present with other lipid disorders (Koeijvoets et al., 2005). Perhaps this might be the case with common variants, which would require the engagement of pediatric populations in this research.

As our understanding of lipid genomics expands, social and behavioral science could take advantage of the change in clinical practice guidelines to better understand how to communicate with pediatric populations, their parents/guardians, and health-care providers. The reason for the change in guidelines was the recognition that early damage to the cardiovascular system was impacting later health. Genetic and environmental factors are written into the guidelines (family history, adolescent smoking). Engaging with these groups about topics in this chapter, such as risk communication, how early identification impacts self-concept, and whether it can positively impact health behavior would move public health genomics in pediatric populations forward. This could be done in the absence of testing and/or by offering FH testing through research protocols. Recruiting this population into G × E studies would also expand our knowledge about the impact of childhood environments on gene expression.

CONCLUSION

Public health genomics is an evolving field. It is still unknown whether genomic risk information will impact behavior change and, if it does, what are the mechanisms by which this occurs (Henrikson et al., 2009). Establishing not only whether but how this information impacts cognitions and behavior, and populations and conditions for which these mechanisms occur, will allow for the most effective integration of this

information into existing behavioral interventions for chronic disease prevention and management. By knowing what "levers to push," this more refined knowledge could increase the likelihood of interventions being successful. Designing and implementing this type of research is a key contribution that social and behavioral scientists can make to the field. Those with specific expertise in pediatric populations can provide insights into the developmental factors that enhance or hinder the integration of such information.

Genomics can potentially decrease the impact of chronic disease by pointing to novel treatments for adult-onset disease or perhaps motivate adults to change health behaviors that impact diseases that they themselves experience. But an even greater impact may be had by elucidating the role of early environment on genomic expression, addressing not only adult behavior change but also, and perhaps more importantly, impact the antecedents of these diseases in early childhood, pointing to behaviors that parents and other decision makers in children's lives should consider. As McBride and Guttmacher (2009) recently noted in regard to the interface of pediatrics and genomic discovery, "families contribute more than genes to their children's health outcomes." More work in this area would allow us to have a better understanding of true primary prevention of disease processes. The availability of these precursors as markers would facilitate intervention earlier in life when there is perhaps a greater chance for long-term health benefit.

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Note: The letters 'f' and 't' following the locators refer to figures and tables respectively

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